Perspectives on percutaneous coronary intervention

Damen, N.L.M.

Publication date:
2014

Document Version
Publisher's PDF, also known as Version of record

PERSPECTIVES ON PERCUTANEOUS CORONARY INTERVENTION: MORE THAN JUST CORONARY ARTERIES?

Nikki L.M. Damen

ISBN: 978-90-9028159-9
Cover design: Elfentaal, www.elfentaal.nl
Lay-out: Sean Straatman
Printing: Printadvise bv, www.printadvise.nl

PERSPECTIVES ON PERCUTANEOUS CORONARY INTERVENTION: MORE THAN JUST CORONARY ARTERIES?

Proefschrift

ter verkrijging van de graad van doctor aan Tilburg University op gezag van de rector magnificus, prof. dr. Ph. Eijlander, in het openbaar te verdedigen ten overstaan van een door het college voor promoties aangewezen commissie in de aula van de Universiteit op vrijdag 23 mei 2014 om 14.15 uur

door

Nikki Laurina Mathilda Damen

geboren op 13 januari 1986 te Etten-Leur

Promotiecommissie

Promotores
Prof. dr. H. Boersma
Prof. dr. S. S. Pedersen

Copromotor
Dr. H. Versteeg

Overige leden
Dr. C. Bode
Prof. dr. G. L. M. van Heck
Dr. H. M. Kupper
Prof. dr. V. J. M. Pop
Dr. K. Redekop
Prof. dr. F. Zijlstra

Het verschijnen van dit proefschrift werd mede mogelijk gemaakt door de steun van de Nederlandse Hartstichting

Paranimfen

Sarah van Giels
Marieke Merkx

"Alles wat groot is, begon ooit klein: je hoeft niet meteen een vlinder te zijn"
Marco Borsato, 'Vlinder' (2004)

TABLE OF CONTENTS

CHAPTER 1 General introduction

"Coronary heart disease is now the leading cause of death worldwide; it is on the rise and has become a true pandemic that respects no borders"
(World Health Organization, 2009)

Cardiovascular disease (CVD) is the leading cause of death in the Western world, with CVD accounting for 32% of all deaths in the United States in 2009 [1]. In the Netherlands, mortality rates are comparable, with 30% of total deaths being attributable to CVD in 2012 [2]. Coronary artery disease (CAD) is one of the most common types of CVD and accounted for nearly half of all cardiovascular deaths, and 1 of every 6 deaths in the United States in 2009 [1]. In the Netherlands, CAD accounted for 25% of all cardiovascular deaths in 2012 [2]. Over the past decades, mortality rates have declined considerably due to improved treatment options, resulting in an increased number of patients living longer with CAD [1, 3]. Hence, CAD imposes a high burden on patients, caregivers, and the health care system worldwide [4]. Despite the decline in mortality rates, CAD is still expected to be the leading cause of death worldwide in 2030 [5], and is number one on the list of projected top 10 diseases with the largest disease burden worldwide in 2020 [6].

CAD, generally caused by atherosclerosis, refers to abnormalities in the coronary arteries that facilitate the supply of blood and oxygen to the heart [7, 8]. Due to plaque growth inside the lumen of coronary arteries, they may become narrowed, which may lead to ischemic chest pain (i.e., angina pectoris). If a coronary artery becomes fully blocked due to plaque rupture and the subsequent formation of thrombosis, this may result in an acute coronary syndrome (ACS), such as myocardial infarction (MI) [7, 8]. In 2009, the prevalence of CAD in the Netherlands was estimated at 5% in men and 3% in women, whereas the annual incidence was 6 per 1000 men and 4 per 1000 women of the Dutch population [9].

CORONARY REVASCULARIZATION PROCEDURES

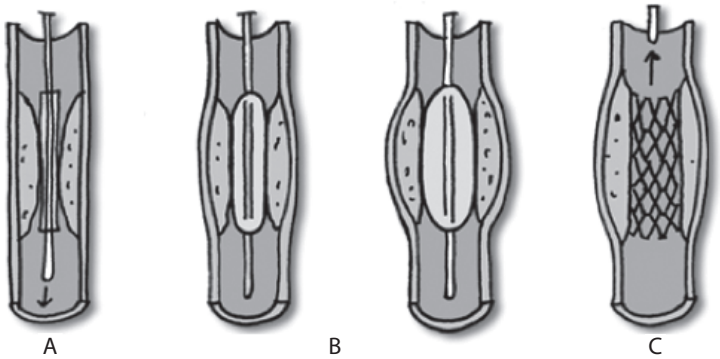
In patients with CAD, coronary revascularization is a common procedure to treat narrowed or obstructed arteries in order to restore coronary blood flow. Coronary artery bypass graft (CABG) surgery and percutaneous coronary intervention (PCI) comprise the 2 primary means of such revascularization [10, 11].

Since its introduction in 1968, CABG surgery rapidly became the treatment of choice for patients with CAD needing revascularization. During CABG surgery, narrowed or obstructed coronary arteries are bypassed by grafting vessels from elsewhere in the body [12]. Usually, "on-pump" CABG surgery is performed, with cardiopulmonary bypass (or heart-lung machine) taking over heart and lung functioning during surgery to maintain

blood and oxygen circulation throughout the body [13]. Over the past decades, there has been growing interest in performing CABG on a beating heart, also referred to as "off-pump surgery" [14].

PCI was introduced by Andreas Grüntzig in 1977 and is a less invasive, non-surgical revascularization procedure [15]. During the first PCI procedures, balloon dilatation was used to dilate the narrowed or obstructed coronary artery, this way restoring coronary blood flow. In 1986, this dilatation procedure was revolutionalized by inserting a "bare"-metal stent in the artery to retain the dilated vessel open (Figure 1). In 2000, the PCI procedure was further improved by the development of the so-called "drug-eluting stent"(DES), which releases a drug in the dilated artery to block cell growth and to reduce the risk for restenosis (i.e., recurrent narrowing or obstruction of the artery) [16]. Previously, restenosis occurred in 30-50% of patients treated with PCI without stenting, whereas this risk decreased to 10-30% with bare-metal stenting. The introduction of DES has further decreased the risk for restenosis and the need for repeated revascularization as compared with bare-metal stenting [17].

Figure 1. Schematic representation of a PCI procedure

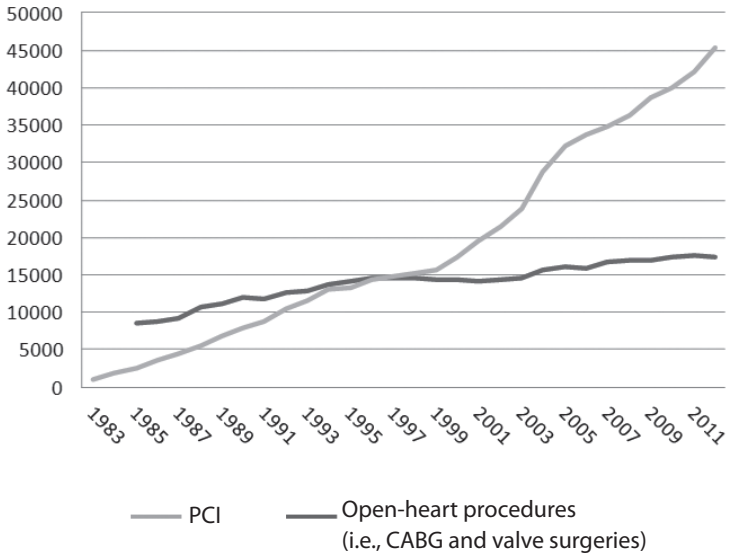


A. Deflated ballon inserted in the affected artery via a cathether
B. Balloon dilatation
C. Stent placement in the dilated artery

Illustrator: Auke Herrema

When PCI was first introduced, this method was thought to be appropriate only for patients with single-vessel disease (i.e., no more than 1 coronary artery being narrowed or obstructed) [15]. Increased experience with this non-surgical procedure and improved technology expanded its use to patients with more complex CAD, such as multi-vessel disease [18]. Today, PCI is the most frequently used revascularization strategy in CAD, with MI, unstable angina pectoris, and stable angina pectoris being common indications [10, 11]. In 2012, 45.305 CAD patients were treated with PCI in the Netherlands, versus 11.240 patients undergoing CABG surgery in that same year [2] (Figure 2).

Figure 2. Nummer of PCI versus open-heart procedures performed in the Netherlands since 1986



Source: Nederlandse Hartstichting, Begeleidingscommissie Hartinterventies Nederland

RISK FACTORS FOR CORONARY ARTERY DISEASE

Traditional risk factors

Hypertension, hypercholesterolemia, smoking, diabetes mellitus, abdominal obesity, physical inactivity, and unhealthy diet have been established as the most important modifiable risk factors for incident CAD and poor prognosis in patients with established CAD, whereas non-modifiable risk factors include age, male gender, and a family history of CAD [1, 19, 20]. Several risk estimation algorithms, such as the Systematic COronary Risk Evaluation (SCORE) algorithm, have been developed to identify persons at high cardiovascular risk [19, 21]. With regard to the prognostic impact of obesity in patients with established CAD, evidence is still inconclusive, as some studies show better survival rates for overweight or obese CAD patients, a phenomenon referred to as the "obesity paradox" [22, 23]. So far, it remains unclear how this phenomenon may be explained.

Psychological risk factors

In addition to traditional biomedical risk factors, there has been growing interest in the role of psychological factors in CAD [19, 24]. Psychological distress is a rather broad concept and refers to a wide range of episodic (e.g., anxiety and depression) and chronic stressors (e.g., personality). Psychological distress is highly prevalent in patients with established CAD, affecting 1 in 4 patients, and has been linked to increased cardiovascular morbidity and mortality [25, 26] and poorer patient-reported outcomes, such as impaired health status and quality of life [27-29]. Health status refers to the patient's perception of the impact of disease or treatment on functional limitations, symptoms, and quality of life, in which quality of life is the discrepancy between actual and desired function [30]. In initially healthy persons, psychological distress has been linked to a higher risk for incident CAD [24].

The identification of patients at high-risk for psychological distress is essential, as it may enhance secondary prevention efforts and point to targets for intervention. The 2012 European Guidelines for Prevention of Cardiovascular Diseases of the European Society of Cardiology state that psychological factors should be assessed in patients with established CAD but also in those at risk for incident CAD [19]. The guidelines specifically refer to anxiety, depression, and the distressed (Type D) personality in their list of recommended psychological risk factors to screen for, which will be discussed in more detail in the subsequent sections. Although over the past decades a vast amount of research focused on the impact of psychological distress on incident CAD as well as its prognostic impact in patients with established CAD, the level of evidence remains moderate (i.e., class IIa indication, level B evidence) and there are still numerous unresolved issues [19].

The role of negative emotions

Most studies on the association between psychological distress and CAD have focused on the role of depression. According to the Diagnostic and Statistic Manual of Mental Disorders, Fifth Edition (DSM-5), depression is characterized by low mood and/or a loss of interest or pleasure in daily activities. These symptoms are often accompanied by a change in appetite or weight, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness and guilt, concentration problems, and suicidal ideation. The presence of at least 5 out of 9 symptoms for most of the day, nearly every day, and for at least 2 weeks, warrants a diagnosis of major depressive disorder (MDD) [31].

The prevalence of depression is high in CAD. Around 20% of patients suffer from MDD after an MI [32], whereas self-reported depressive symptoms are prevalent in 25-50% of CAD patients [26, 32, 33]. These rates are approximately 3 times higher than rates reported in the general population [32]. A recent meta-analysis confirmed that depression is associated with a 1.6 to 2.7-fold increased risk for all-cause mortality and adverse cardiac events up to 2 years post-MI, independent of disease severity [26]. Besides, depression has been associated with impaired health status [27, 29, 34], poor adherence to treatment [35, 36], and increased health care consumption [37] in patients with established CAD.

Anxiety comprises the second most frequently studied psychological distress factor in the context of CAD. Anxiety refers to feelings of fear, worry, and uneasiness in response to a perceived threat [31], often resulting from a sense of being unable to predict, control, or obtain a desired outcome [38]. Anxiety is often accompanied by increased activity of the autonomic nervous system and ranges along a continuum from normal to pathological [31]. Pathological anxiety, or anxiety disorders, include among others generalized anxiety disorder, panic disorder, agoraphobia, post-traumatic stress disorder, specific phobia, and social phobia [31].

Around 45% of patients with CAD present with an anxiety disorder at some point in their life [39], whereas self-reported anxiety symptoms are observed in 20-60% of CAD patients [25]. Although anxiety is highly prevalent in patients with CAD, its impact on prognosis is less clear. According to recent meta-analyses, anxiety is associated with a 1.2 to 1.7-fold increased risk of cardiovascular morbidity and mortality in CAD patients who suffered an MI [25]. However, in other studies no such associations [40, 41] or even protective effects of anxiety on survival were reported in patients with established CAD [42-44]. The better survival rates in anxious patients may be attributed to a more optimal help-seeking pattern for somatic complaints in (non-phobic) anxious patients. It is known that anxious patients are more likely to receive coronary angiography even in the presence of less severe or insignificant CAD, which could facilitate earlier initiation of adequate treatment. Further, in contrast to depressed patients, anxious patients may be more motivated to

control their CAD risk factors and have a better adherence to treatment [37, 42, 43]. However, evidence on this topic is scarce and conflicting, as poor adherence to treatment and life style recommendations has also been reported in anxious MI patients [45, 46]. Finally, like depression, anxiety has been associated with poorer patient-reported outcomes in patients with CAD, including impaired health status and quality of life [27, 29, 47].

Type D personality

Besides episodic stressors, such as anxiety and depression, personality traits have been linked to CAD outcomes. Type D personality is a commonly investigated trait in this context, which originates from clinical and research work on Belgian CAD patients attending cardiac rehabilitation [48]. The construct focuses on the differential effect of individual coping styles on emotional and physical health [49], and how the interaction between different personality traits may affect prognosis [50]. Type D personality is composed of 2 broad personality traits: Negative affectivity (NA) and social inhibition (SI). Individuals scoring high on negative affectivity tend to experience negative emotions (e.g., feeling down in the dumps) across time and situations, while individuals scoring high on social inhibition tend not to express these negative emotions in social situations out of fear of rejection or disapproval [48].

Type D personality is prevalent in 25-37% of CAD patients [48, 51]. Evidence suggests that CAD patients with a Type D personality are 1.4 to 3.7 times more likely to die and to experience adverse cardiac events as compared with non-Type D patients [52, 53]. Further, Type D personality is associated with increased anxiety and depression [54-56], impaired health status [28], and poor medication adherence [57, 58]. However, in a recent meta-analysis, the authors concluded that although there is a significant association between Type D personality and prognosis in cardiac patients, the strength of this effect has been declining over the years and that therefore, the effect of Type D might have been overestimated in previous studies [59]. Further, an effect for Type D personality on prognosis was mainly found in CAD patients with acute coronary syndromes, such as post-MI and CABG patients, but not in heart failure patients [59].

Another avenue to pursue: The role of positive emotions

In contrast to the vast amount of research focusing on the impact of negative emotions on CAD outcomes, the role of positive emotions has received less attention [60, 61]. Positive affect refers to mood states such as joy, activity, and cheerfulness [62], and is not merely the opposite of negative affect [63], as both types of affect can be present simultaneously [64]. High levels of positive affect have been associated with a decrease in hospital readmissions in patients with established CAD [65], lower incident hypertension [66], and lower incident CAD [67], while studies on the association between positive affect and survival have shown mixed results [61, 68, 69]. Only a paucity of studies focused on the impact of anhedonia (i.e.,

reduced positive affect) on CAD outcomes, indicating that anhedonia is associated with a higher risk for mortality and adverse cardiac events up to 2 years follow-up [60, 70] as well as with poorer patient-reported outcomes, such as impaired health status [71, 72].

Potential underlying mechanisms

Several potential pathways have been proposed as underlying mechanisms for the relationship between psychological distress and poor prognosis in CAD. Biological pathways include the hypothalamus-pituitary-adrenal axis [73, 74], autonomic nervous system functioning [75, 76], coronary plaque burden [77, 78], and inflammation [79]. In addition, behavioral pathways have been suggested, with psychologically distressed patients being less likely to engage in optimal health-related behaviors, such as exercising, quitting smoking, and adhering to dietary advice [75, 80, 81]. These potential pathways largely remain speculative, as few studies have examined these pathways as potential links between psychological distress and prognosis in CAD, and results being inconsistent.

CURRENT KNOWLEDGE GAPS

Although considerable literature is available on the role of psychological distress in CAD, demonstrating that negative emotions, such as anxiety, depression, and Type D personality, are highly prevalent in CAD patients and associated with adverse clinical and patient-reported outcomes, several knowledge gaps can be identified.

There is a gap in our understanding of the impact of psychological distress on long-term prognosis in CAD patients, as on average follow-up durations of previous studies ranged between 1.5 and 2.5 years [25, 26]. Further, there has been a tendency in the literature to focus on one psychological risk factor at a time, which has also been labeled as the 'risk factor of the month approach' [82]. The question remains whether psychological distress factors, such as anxiety and depression, exert an independent effect on prognosis in CAD or whether other psychological factors may explain some of the variance of these associations, as they are often inter-related and co-occur [82, 83]. In addition, the majority of studies focusing on the prognostic impact of episodic psychological risk factors do not take into account the role of more stable factors, such as personality [83]. Finally, the mechanisms through which psychological distress may lead to poorer prognosis in CAD remain unclear, warranting more research, as this knowledge may facilitate the development of successful psychological intervention trials in the future.

From a methodological point of view, we know little about the occurrence of attrition bias in studies on patients with CAD and the associated consequences for conclusions drawn. The majority of previous studies examining the prevalence of psychological factors and their impact on clinical outcome in CAD patients used a

prospective cohort design in combination with standardized and validated questionnaires as the primary methodology [25, 26, 28, 59]. A potential attrition bias can be introduced if patients who complete the study ("completers") versus patients who are lost to follow-up ("drop-outs") differ systematically on baseline characteristics, exposure to risk factors, or outcome variables [84], jeopardizing the conclusions drawn - as there may be an over- or underestimation of the true effect - and the generalizability [85]. However, we know little about differences between completers and drop-outs, as most previous prospective studies do not report drop-out rates, reasons for drop-out, or compare the characteristics of drop-outs versus completers [86].

So far, the majority of previous studies on psychological distress in CAD have focused on post-MI, CABG, or general CAD patients. Despite PCI being currently the most commonly used coronary revascularization procedure, few studies have focused on the patient perspective in PCI. Although MI patients account for a substantial part of the PCI population, unstable and stable angina pectoris are also common indications. A previous study in admitted unstable angina pectoris patients identified depression in 41% of patients and showed that depressed angina patients were more than 6 times more likely to experience an adverse cardiac event as compared with non-depressed patients [87]. Little is known about the impact of psychological distress in PCI patients, including broad indications ranging from stable and unstable angina to MI, and whether it is similar to that reported in post-MI, CABG, and general CAD populations, or whether disease- and treatment-specific processes play a role in this context.

THE CURRENT DISSERTATION: FOCUS ON PATIENTS TREATED WITH PCI

The current dissertation extends previous research by focusing on the psychological well-being of patients treated with PCI and the impact of psychological distress on long-term survival in this specific patient group. Further, the current dissertation will briefly tap into potential underlying mechanisms that may explain the link between psychological distress and poorer prognosis in patients treated with PCI and addresses the issue of attrition bias in prospective cohort studies and its potential consequences for study conclusions.

Except for *Chapter 10*, all studies presented in this dissertation are based on data collected in the Erasmus MC, Rotterdam, the Netherlands. In total, 4 cohorts of patients treated with PCI between 2001 and 2011 are included (Table 1). In *Chapter 10,* data from the national Danish Heart Registry was used to identify patients admitted to Danish hospitals with a first-time CABG surgery or PCI procedure between 1999 and 2012.

Table 1. Overview of the cohorts of PCI patients and patient-reported measures used in the current dissertation

	Inclusion period	***Type of stent***	***Patient-reported measures***	***Instruments***	***Chapters***
Cohort 1 *Subsample of the RESEARCH registry*	Sept 2001 – Nov 2002	BMS or SES	Anxiety Depression Type D personality Health status	HADS HADS DS14 SF-36	4, 5, 6
Cohort 2	July 2003 – July 2004	PES	Anxiety Depression Type D personality	HADS HADS DS14	2, 3, 9
Cohort 3	Feb 2006 – Sept 2006	PES	Anxiety Depression Type D personality Remembered parenting	HADS HADS DS14 RRP[10]	2, 3, 7, 9
Cohort 4	Feb 2009 – Jan 2011*	EES	Anxiety Depression Type D personality	STAI-S PHQ-9 DS14	8

BMS = Bare-metal stent, DS14 = Type D scale, EES = everolimus-eluting stent, HADS = Hospital Anxiety and Depression Scale, PES = paclitaxel-eluting stent, PHQ-9 = 9-item Patient Health Questionnaire, RRP[10] = Remembered Relationship with Parents scale, SES = sirolimus-eluting stent, SF-36 = 36-item Short-Form Health Survey, STAI-S = State measure of the State-Trait Anxiety Inventory

* Data was partly gathered by Nikki Damen from Sept 2010 – May 2012

Aims and outline of this dissertation

As aforementioned, indications for PCI include MI, unstable angina pectoris, and stable angina pectoris [10]. One might expect that MI patients undergoing a PCI procedure experience higher levels of anxiety and depression than those with unstable angina pectoris or stable angina pectoris, due to the more acute nature of the cardiac event. To date, little is known about the influence of indication for PCI on psychological distress [54]. Hence, the aim of *Chapter 2* is to examine the association between indication for PCI (i.e., MI, unstable angina pectoris, or stable angina pectoris) and anxiety and depression levels in the first year post-PCI.

When examining anxiety and depression levels in cardiac patients this is generally done by means of incidence and prevalence rates [88], or changes in overall mean scores over time [54]. However, these approaches mask intra-individual changes over time and, consequently, potential differential risks of adverse health outcomes may be overlooked [89]. *Chapter 3* reports on changes in anxiety and depression over a 12-month period post-PCI using an intra-individual approach, and identifies the demographic and clinical correlates of these changes.

Although substantial research has focused on the association between depression and mortality in CAD, only a paucity of studies examined the impact of depression on long-term mortality (≥5 years), with results being inconsistent [33, 42, 90]. To our knowledge, no such studies are available in PCI patients. Hence, in *Chapter 4* we study the association between depression and long-term mortality with a median follow-up duration of 7 years post-PCI. Given that there has been a tendency in the literature to focus on one psychological risk factor at a time, also called 'risk factor of the month approach' [82], we also examine whether the effect of depression on mortality is independent of anxiety and Type D personality. In relation to Chapter 4, a letter to the editor and our reply have been added at the end of the chapter.

A paucity of studies focused on the impact of anhedonia on short-term prognosis [60, 70], but it is not yet known whether anhedonia is associated with long-term prognosis. Hence, in *Chapter 5,* the impact of anhedonia on long-term mortality with a median follow-up duration of 7 years post-PCI is presented.

Medical explanations, such as differences in medication prescriptions [23, 91], do not provide a clear understanding of the obesity paradox, which refers to the better survival rates reported in overweight or obese CAD patients [27, 28]. Impaired health status has been linked to poor prognosis in CAD [92, 93] and a paucity of studies focused on the association between

obesity and health status [94, 95], but the role of health status in the context of obesity and mortality in CAD has not yet been examined. Hence, in *Chapter 6* we pursue health status as a potential explanation for the obesity paradox in patients treated with PCI.

Both Type D personality and dysfunctional parenting styles, like overprotection or coldness, are associated with anxiety and depression [54, 96]. As parenting styles have been related to personality development [97, 98], dysfunctional parenting styles may also be associated with Type D personality, which in turn may increase the risk for anxiety and depression. *Chapter 7* examines whether remembered parenting is associated with anxiety and depression in cardiac patients and whether Type D personality mediates this relationship.

Chapter 8 elaborates on inflammation and coronary plaque burden as potential mechanisms underlying the relationship between psychological distress and prognosis in patients treated with PCI. More specifically, in this cross-sectional study we examined whether psychological distress is associated with selected inflammatory markers or the extent of coronary plaque burden, as measured by intravascular ultrasound [99].

In the majority of previous studies as well as in the current dissertation, the prospective cohort design in combination with standardized and validated questionnaires has been the primary methodology used to examine a link between psychological factors and CAD outcomes [25, 26, 28, 59]. *Chapter 9* investigates the possible occurrence and consequence of attrition bias in a prospective cohort study by examining differences in socio-demographic, clinical, and psychological (i.e., anxiety, depression, and Type D personality) baseline characteristics, and 4-year risk for all-cause mortality between completers and drop-outs at 12 months in patients treated with PCI.

Besides PCI, CABG surgery is a commonly performed coronary revascularization strategy [10, 11]. Little is known about potential differences in patient well-being between CABG and PCI patients. A more invasive procedure may be associated with increased use of psychopharmaca. Hence, the aim of *Chapter 10* is to prospectively examine differences in antidepressant and anxiolytic medication use between CABG and PCI patients up to 12 months post-index event, using data from the national Danish Heart Registry.

Finally, in *Chapter 11* the main findings of this dissertation are discussed and implications for future research and clinical practice are outlined.

REFERENCES

1. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics—2013 update: A report from the American Heart Association. Circulation. 2013;127(1):e6-e245.
2. Vaartjes I, Koopman C, van Dis I, Visseren FLJ, Bots ML. Hart-en vaatziekten in Nederland 2013. Den Haag: Nederlandse Hartstichting; 2013.
3. Mackay J, Mensah G. The atlas of heart disease and stroke. World Health Organization; 2004.
4. Leal J, Luengo-Fernández R, Gray A, Petersen S, Rayner M. Economic burden of cardiovascular diseases in the enlarged European Union. Eur Heart J. 2006;27(13):1610-9.
5. World Health Organization. World Health Statistics 2008. World Health Organization; 2008.
6. Michaud CM, Murray CL, Bloom BR. Burden of disease—Implications for future research. J Am Med Assoc. 2001;285(5):535-9.
7. Scarborough P, Bhatnager P, Wickramasinghe K, Smolina K, Mitchell C, Rayner M. Coronary heart disease statistics 2010. UK: Britisch Heart Foundation; 2010.
8. National-Heart-Lung-and-Blood-Institute. What is coronary heart disease? Available at: http://www.nhlbi.nih.gov/health/health-topics/topics/cad. Accessed August 9, 2013.
9. Vaartjes I, van Dis I, Visseren FLJ, Bots ML. Hart-en vaatziekten in Nederland 2010. Den Haag: Nederlandse Hartstichting; 2010.
10. Silber S, Albertsson P, Avilés FF, Camici PG, Colombo A, Hamm C, et al. Guidelines for percutaneous coronary interventions: The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. Eur Heart J. 2005;26(8):804-47.
11. Kushner FG, Hand M, Smith Jr SC, King Iii SB, Anderson JL, Antman EM, et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update): A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2009;54(23):2205-41.
12. Favaloro RG. Saphenous vein autograft replacement of severe segmental coronary artery occlusion: Operative technique. Ann Thorac Surg. 1968;5(4):334-9.
13. Favaloro RG. The aortocoronary bypass. The challenging dream of heart surgery. Boston, Mass: Little Brown Company; 1994.
14. Mitka M. Beat goes on in "off-pump" bypass surgery. J Am Med Assoc. 2004;291(15):1821-2.
15. Grüntzig AR, Senning Å, Siegenthaler WE. Nonoperative dilatation of coronary-artery stenosis. N Engl J Med. 1979;301(2):61-8.
16. Meier B. 25 years of coronary angioplasty: Almost a fairy tale. Lancet. 2003;361(9356):527.
17. Weintraub WS. The pathophysiology and burden of restenosis. Am J Cardiol. 2007;100(5, Supplement):S3-S9.
18. Mohr FW, Morice M, Kappetein AP, Feldman TE, Ståhle E, Colombo A, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. Lancet. 2013;381(9867):629-38.
19. Perk J, de Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J. 2012;33(13):1635-701.
20. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. Lancet. 2004;364(9438):937-52.

21. Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, de Backer G, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: The SCORE project. Eur Heart J. 2003;24(11):987-1003.
22. Hastie CE, Padmanabhan S, Slack R, Pell AC, Oldroyd KG, Flapan AD, et al. Obesity paradox in a cohort of 4880 consecutive patients undergoing percutaneous coronary intervention. Eur Heart J. 2010;31(2):222-6.
23. Gruberg L, Mercado N, Milo S, Boersma E, Disco C, van Es GA, et al. Impact of body mass index on the outcome of patients with multivessel disease randomized to either coronary artery bypass grafting or stenting in the ARTS trial: The obesity paradox II? Am J Cardiol. 2005;95(4):439-44.
24. Rosengren A, Hawken S, Ounpuu S, Sliwa K, Zubaid M, Almahmeed WA, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): Case-control study. Lancet. 2004;364(9438):953-62.
25. Roest AM, Martens EJ, Denollet J, de Jonge P. Prognostic association of anxiety post myocardial infarction with mortality and new cardiac events: A meta-analysis. Psychosom Med. 2010;72(6):563-9.
26. Meijer A, Conradi HJ, Bos EH, Thombs BD, van Melle JP, de Jonge P. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: A meta-analysis of 25 years of research. Gen Hosp Psychiatry. 2011;33(3):203-16.
27. Lane D, Carroll D, Ring C, Beevers DG, Lip GYH. Mortality and quality of life 12 months after myocardial infarction: Effects of depression and anxiety. Psychosom Med. 2001;63(2):221-30.
28. Versteeg H, Spek V, Pedersen SS, Denollet J. Type D personality and health status in cardiovascular disease populations: A meta-analysis of prospective studies. Eur J Cardiovasc Prev Rehabil. 2011;19(6):1373-80.
29. Sullivan MD, LaCroix AZ, Spertus JA, Hecht J. Five-year prospective study of the effects of anxiety and depression in patients with coronary artery disease. Am J Cardiol. 2000;86(10):1135-8.
30. Spertus JA. Evolving applications for patient-centered health status measures. Circulation. 2008;118(20):2103-10.
31. American Psychiatric Association. Diagnostic and statistic manual of mental disorders, fifth edition. American Psychiatric Publishing; 2013.
32. Thombs BD, Bass EB, Ford DE, Stewart KJ, Tsilidis KK, Patel U, et al. Prevalence of depression in survivors of acute myocardial infarction. J Gen Intern Med. 2006;21(1):30-8.
33. Connerney I, Sloan RP, Shapiro PA, Bagiella E, Seckman C. Depression is associated with increased mortality 10 years after coronary artery bypass surgery. Psychosom Med. 2010;72(9):874-81.
34. Ruo B, Rumsfeld JS, Hlatky MA, Liu H, Browner WS, Whooley MA. Depressive symptoms and health-related quality of life: The Heart and Soul Study. J Am Med Assoc. 2003;290(2):215-21.
35. Rieckmann N, Gerin W, Kronish IM, Burg MM, Chaplin WF, Kong G, et al. Course of depressive symptoms and medication adherence after acute coronary syndromes: An electronic medication monitoring study. J Am Coll Cardiol. 2006;48(11):2218-22.
36. DiMatteo M, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: Meta-analysis of the effects of anxiety and depression on patient adherence. Arch Int Med. 2000;160(14):2101-7.
37. Strik JJMH, Denollet J, Lousberg R, Honig A. Comparing symptoms of depression and anxiety as predictors of cardiac events and increased health care consumption after myocardial infarction. J Am Coll Cardiol. 2003;42(10):1801-7.
38. Barlow DH. Unraveling the mysteries of anxiety and its disorders from the perspective of emotion theory. Am Psychol. 2000;55(11):1247-63.
39. Todaro JF, Shen BJ, Raffa SD, Tilkemeier PL, Niaura R. Prevalence of anxiety disorders in men and women with established coronary heart disease. J Cardiopulm Rehabil Prev. 2007;27(2):86-91.
40. Lane D, Carroll D, Ring C, Beevers DG, Lip GYH. Do depression and anxiety predict recurrent coronary events 12 months after myocardial infarction? QJM. 2000;93(11):739-44.

41. Levine JB, Covino NA, Slack WV, Safran C, Safran DB, Boro JE, et al. Psychological predictors of subsequent medical care among patients hospitalized with cardiac disease. J Cardiopulmon Rehabil Prev. 1996;16(2):109-16.
42. Herrmann C, Brand-Driehorst S, Buss U, Rüger U. Effects of anxiety and depression on 5-year mortality in 5057 patients referred for exercise testing. J Psychosom Res. 2000;48(4-5):455-62.
43. Meyer T, Buss U, Herrmann-Lingen C. Role of cardiac disease severity in the predictive value of anxiety for all-cause mortality. Psychosom Med. 2010;72(1):9-15.
44. Mykletun A, Bjerkeset O, Dewey M, Prince M, Overland S, Stewart R. Anxiety, depression, and cause-specific mortality: The HUNT study. Psychosom Med. 2007;69(4):323-31.
45. Benninghoven D, Kaduk A, Wiegand U, Specht T, Kunzendorf S, Jantschek G. Influence of anxiety on the course of heart disease after acute myocardial infarction - Risk factor or protective function? Psychother Psychosom. 2006;75(1):56-61.
46. Kuhl EA, Fauerbach JA, Bush DE, Ziegelstein RC. Relation of anxiety and adherence to risk-reducing recommendations following myocardial infarction. Am J Cardiol. 2009;103(12):1629-34.
47. Pedersen SS, Denollet J, Spindler H, Ong ATL, Serruys PW, Erdman RAM, et al. Anxiety enhances the detrimental effect of depressive symptoms on health status following percutaneous coronary intervention. J Psychosom Res. 2006;61(6):783-9.
48. Denollet J. DS14: Standard assessment of negative affectivity, social inhibition, and Type D personality. Psychosom Med. 2005;67(1):89-97.
49. Denollet J. Negative affectivity and repressive coping: Pervasive influence on self-reported mood, health, and coronary-prone behavior. Psychosom Med. 1991;53(5):538-56.
50. Denollet J, Sys SU, Brutsaert DL. Personality and mortality after myocardial infarction. Psychosom Med. 1995;57(6):582-91.
51. Kupper N, Pedersen SS, Höfer S, Saner H, Oldridge N, Denollet J. Cross-cultural analysis of Type D (distressed) personality in 6222 patients with ischemic heart disease: A study from the International HeartQoL Project. Int J Cardiol. 2013;166(2):327-33.
52. Denollet J, Pedersen SS, Vrints CJ, Conraads VM. Predictive value of social inhibition and negative affectivity for cardiovascular events and mortality in patients with coronary artery disease: The Type D personality construct. Psychosom Med. 2013;75(9):873-81.
53. Denollet J, Schiffer AA, Spek V. A general propensity to psychological distress affects cardiovascular outcomes. Circ Cardiovasc Qual Outcomes. 2010;3(5):546-57.
54. van Gestel YRBM, Pedersen SS, van de Sande M, de Jaegere PPT, Serruys PW, Erdman RAM, et al. Type-D personality and depressive symptoms predict anxiety 12 months post-percutaneous coronary intervention. J Affect Disord. 2007;103(1):197-203.
55. Pedersen SS, Ong ATL, Sonnenschein K, Serruys PW, Erdman RAM, van Domburg RT. Type D personality and diabetes predict the onset of depressive symptoms in patients after percutaneous coronary intervention. Am Heart J. 2006;151(2):367.e1-376.e6.
56. Bunevicius A, Brozaitiene J, Staniute M, Gelziniene V, Duoneliene I, Pop VJ, et al. Decreased physical effort, fatigue, and mental distress in patients with coronary artery disease: Importance of personality-related differences. Int J Behav Med. 2013; In press, doi: 10.1007/s12529-013-9299-9.
57. Williams L, O'Connor RC, Grubb N, O'Carroll R. Type D personality predicts poor medication adherence in myocardial infarction patients. Psychol Health. 2011;26(6):703-12.
58. Molloy GJ, Randall G, Wikman A, Perkins-Porras L, Messerli-Bürgy N, Steptoe A. Type D personality, self-efficacy, and medication adherence following an acute coronary syndrome. Psychosom Med. 2012;74(1):100-6.
59. Grande G, Romppel M, Barth J. Association between Type D personality and prognosis in patients with cardiovascular diseases: A systematic review and meta-analysis. Ann Behav Med. 2012;43(3):299-310.
60. Denollet J, Pedersen SS, Daemen J, de Jaegere P, Serruys PW, van Domburg RT. Reduced positive affect (anhedonia) predicts major clinical events following implantation of coronary-artery stents. J Intern Med. 2008;263(2):203-11.

61. Brummett BH, Boyle SH, Siegler IC, Williams RB, Mark DB, Barefoot JC. Ratings of positive and depressive emotion as predictors of mortality in coronary patients. Int J Cardiol. 2005;100(2):213-6.
62. Pressman SD, Cohen S. Does positive affect influence health? Psychol Bull. 2005;131:925-71.
63. Tellegen A, Watson D, Clark LA. On the dimensional and hierarchical structure of affect. Psychol Sci. 1999;10(4):297-303.
64. Larsen JT, McGraw AP, Cacioppo JT. Can people feel happy and sad at the same time? J Pers Soc Psychol. 2001;81(4):684-96.
65. Middleton R, Byrd K. Psychosocial factors and hospital readmission status of older persons with cardiovascular disease. J Appl Rehabil Counsel. 1996;27:3-10.
66. Smart Richmann L, Kubzansky L, Maselko J, Kawachi I, Choo P, Bauer M. Positive emotion and health: Going beyond the negative. Health Psychol. 2005;24(4):422-9.
67. Davidson KW, Mostofsky E, Whang W. Don't worry, be happy: Positive affect and reduced 10-year incident coronary heart disease: The Canadian Nova Scotia Health Survey. Eur Heart J. 2010;31(9):1065-70.
68. Kubzansky LD, Sparrow D, Vokonas P, Kawachi I. Is the glass half empty or half full? A prospective study of optimism and coronary heart disease in the normative aging study. Psychosom Med. 2001;63(6):910-6.
69. Hoen PW, Denollet J, de Jonge P, Whooley MA. Positive affect and survival in patients with stable coronary heart disease: Findings from the Heart and Soul Study. J Clin Psychiatry. 2013;74(7):716-22.
70. Davidson KW, Burg MM, Kronish IM, Shimbo D, Dettenborn L, Mehran R, et al. Association of anhedonia with recurrent major adverse cardiac events and mortality 1 year after acute coronary syndrome. Arch Gen Psychiatry. 2010;67(5):480-8.
71. Versteeg H, Pedersen SS, Erdman RAM, van Nierop J, de Jaegere P, van Domburg RT. Negative and positive affect are independently associated with patient-reported health status following percutaneous coronary intervention. Qual Life Res. 2009;18(8):953-60.
72. Pelle AJ, Pedersen SS, Erdman RAM, Kazemier M, Spiering M, van Domburg RT, et al. Anhedonia is associated with poor health status and more somatic and cognitive symptoms in patients with coronary artery disease. Qual Life Res. 2010;20(5):643-51.
73. Jokinen J, Nordström P. HPA axis hyperactivity and cardiovascular mortality in mood disorder inpatients. J Affect Disord. 2009;116(1 2):88-92.
74. Brown ES, Varghese FP, McEwen BS. Association of depression with medical illness: Does cortisol play a role? Biol Psychiatry. 2004;55(1):1-9.
75. Carney RM, Freedland KE, Miller GE, Jaffe AS. Depression as a risk factor for cardiac mortality and morbidity: A review of potential mechanisms. J Psychosom Res. 2002;53(4):897-902.
76. Martens EJ, Nyklíček I, Szabó BM, Kupper N. Depression and anxiety as predictors of heart rate variability after myocardial infarction. Psychol Med. 2008;38(3):375-83.
77. Seldenrijk A, Vogelzangs N, van Hout HPJ, van Marwijk HWJ, Diamant M, Penninx BWJH. Depressive and anxiety disorders and risk of subclinical atherosclerosis: Findings from the Netherlands Study of Depression and Anxiety (NESDA). J Psychosom Res. 2010;69(2):203-10.
78. Tiemeier H, van Dijck W, Hofman A, Witteman JM, Stijnen T, Breteler MB. Relationship between atherosclerosis and late-life depression: The Rotterdam study. Arch Gen Psychiatry. 2004;61(4):369-76.
79. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: A meta-analysis. Psychosom Med. 2009;71(2):171-86.
80. Gilmour J, Williams L. Type D personality is associated with maladaptive health-related behaviours. J Health Psychol. 2012;17(4):471-8.
81. Dempe C, Jünger J, Hoppe S, Katzenberger M, Möltner A, Ladwig KH, et al. Association of anxious and depressive symptoms with medication nonadherence in patients with stable coronary artery disease. J Psychosom Res. 2013;74(2):122-7.

82. Rozanski A, Blumenthal JA, Davidson KW, Saab PG, Kubzansky L. The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: The emerging field of behavioral cardiology. J Am Coll Cardiol. 2005;45(5):637-51.
83. Denollet J, Brutsaert DL. Personality, disease severity, and the risk of long-term cardiac events in patients with a decreased ejection fraction after myocardial infarction. Circulation. 1998;97(2):167-73.
84. Jousilahti P, Salomaa V, Kuulasmaa K, Niemelä M, Vartiainen E. Total and cause specific mortality among participants and non-participants of population based health surveys: A comprehensive follow up of 54 372 Finnish men and women. J Epidemiol Commun Health. 2005;59(4):310-5.
85. Wolke D, Waylen A, Samara M, Steer C, Goodman R, Ford T, et al. Selective drop-out in longitudinal studies and non-biased prediction of behaviour disorders. Br J Psychiatry. 2009;195(3):249-56.
86. Demark-Wahnefried W, Bowen DJ, Jabson JM, Paskett ED. Scientific bias arising from sampling, selective recruitment, and attrition: The case for improved reporting. Cancer Epidemiol Biomarkers Prev. 2011;20(3):415-8.
87. Lespérance F, Frasure-Smith N, Juneau M, Théroux P. Depression and 1-year prognosis in unstable angina. Arch Intern Med. 2000;160(9):1354-60.
88. Blumenthal JA, Lett HS, Babyak MA, White W, Smith PK, Mark DB, et al. Depression as a risk factor for mortality after coronary artery bypass surgery. Lancet. 2003;362(9384):604-9.
89. Kaptein KI, de Jonge P, van den Brink RHS, Korf J. Course of depressive symptoms after myocardial infarction and cardiac prognosis: A latent class analysis. Psychosom Med. 2006;68(5):662-8.
90. Parakh K, Thombs BD, Fauerbach JA, Bush DE, Ziegelstein RC. Effect of depression on late (8 years) mortality after myocardial infarction. Am J Cardiol. 2008;101(5):602-6.
91. Steinberg BA, Cannon CP, Hernandez AF, Pan W, Peterson ED, Fonarow GC. Medical therapies and invasive treatments for coronary artery disease by body mass: The "obesity paradox" in the Get With The Guidelines database. Am J Cardiol. 2007;100(9):1331-5.
92. Mommersteeg PM, Denollet J, Spertus JA, Pedersen SS. Health status as a risk factor in cardiovascular disease: A systematic review of current evidence. Am Heart J. 2009;157(2):208-18.
93. Schenkeveld L, Pedersen SS, van Nierop JWI, Lenzen MJ, de Jaegere PPT, Serruys PW, et al. Health-related quality of life and long-term mortality in patients treated with percutaneous coronary intervention. Am Heart J. 2010;159(3):471-6.
94. Evangelista LS, Moser DK, Westlake C, Hamilton MA, Fonarow GC, Dracup K. Impact of obesity on quality of life and depression in patients with heart failure. Eur J Heart Fail. 2006;8(7):750-5.
95. Oreopoulos A, Padwal R, McAlister FA, Ezekowitz J, Sharma AM, Kalantar-Zadeh K, et al. Association between obesity and health-related quality of life in patients with coronary artery disease. Int J Obes. 2010;34(9):1434-41.
96. Denollet J, Smolderen KGE, van den Broek KC, Pedersen SS. The 10-item Remembered Relationship with Parents (RRP10) scale: Two-factor model and association with adult depressive symptoms. J Affect Disord. 2007;100(1–3):179-89.
97. Aron EN, Aron A, Davies KM. Adult shyness: The interaction of temperamental sensitivity and an adverse childhood environment. Pers Soc Psychol Bull. 2005;31(2):181-97.
98. Enns MW, Cox BJ, Larsen DK. Perceptions of parental bonding and symptom severity in adults with depression: Mediation by personality dimensions. Can J Psychiatry. 2000;45(3):263-8.
99. de Boer SPM, Cheng JM, Garcia-Garcia HM, Oemrawsingh RM, van Geuns RJ, Regar E. Relation of genetic profile and novel circulating biomarkers with coronary plaque phenotype as determined by intravascular ultrasound: Rationale and design of the ATHEROREMO-IVUS study. EuroIntervention. 2013; In press; pii: 20130113-01.

CHAPTER 2

Indication for percutaneous coronary intervention is not associated with symptoms of anxiety and depression

Damen NL, Versteeg H, Boersma E, de Jaegere PP, van Geuns RM, van Domburg RT, Pedersen SS. Int J Cardiol. 2013;168(5):4897-8.
Short report

Percutaneous coronary intervention (PCI) is one of the mainstays of treatment for patients with coronary artery disease (CAD). Indications for PCI include myocardial infarction (MI), unstable angina pectoris (UAP), and stable angina pectoris (SAP). Previous studies have demonstrated that PCI indication is associated with different cardiovascular morbidity and mortality rates [1, 2].

Anxiety and depression are prevalent in 25-50% of CAD patients [3-5] and are associated with poor prognosis [3, 4], impaired health-related quality of life (HRQOL) [5], and increased health-care consumption [4]. A paucity of studies examined the association between indication for treatment and levels of psychological distress in cardiac patients, with these studies mainly focusing on acute coronary syndrome (ACS) [6-8] and implantable cardioverter defibrillator (ICD) patients [9], and results being inconsistent.

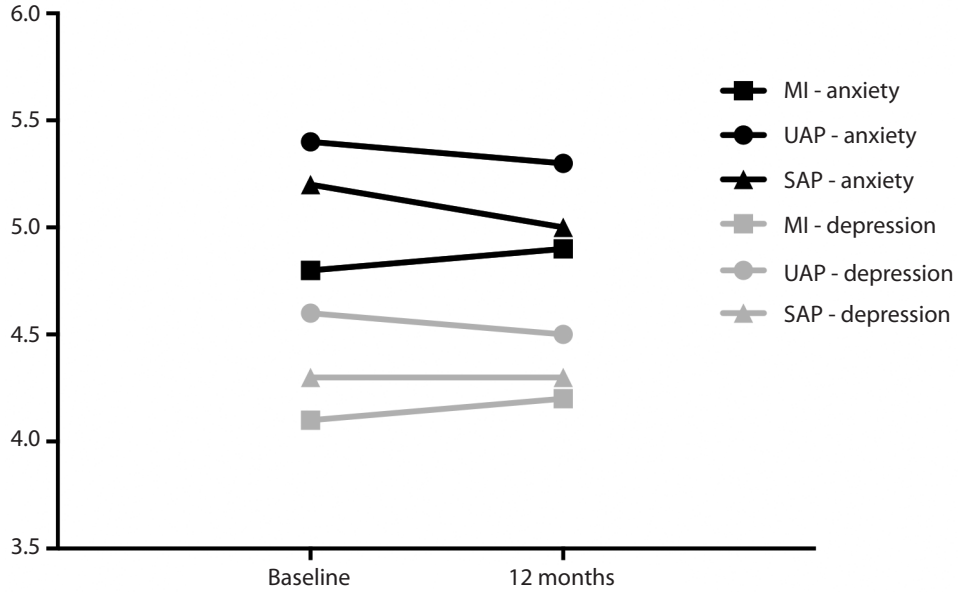
Although some studies focusing on predictors of anxiety and depression post-PCI included PCI indication in their multivariable models [10, 11], the independent contribution of this factor on psychological distress levels over time is still unclear. One might expect that MI patients undergoing PCI experience higher levels of anxiety and depression than those with UAP or SAP, due to the more acute nature of the cardiac event. If confirmed, this could point to targets for the identification and management of psychological distress in PCI patients. Hence, the aim of the current prospective cohort study was to examine the association between indication for PCI (i.e., PCI for MI, UAP, or SAP, respectively) and anxiety and depression levels in the first year post-PCI.

Our sample comprised 791 consecutive patients (76.9% men; mean age 63.3±10.7 years, range [30-87] years) who underwent PCI between July 1, 2003 and September 14, 2006 at the Erasmus MC, Rotterdam, the Netherlands. At baseline (i.e., 4 weeks post-PCI) and 12 months post-PCI, patients completed the Dutch version of the Hospital Anxiety and Depression Scale (HADS) to assess symptoms of anxiety and depression [12]. Information on socio-demographic and clinical variables was systematically collected at the time of the index-PCI (baseline) and recorded in our institutional database.

The association between indication for PCI and anxiety and depression levels was examined by analysis of variance (ANOVA) for repeated-measures with indication (i.e., MI, UAP, and SAP) entered as a between-subject factor. Analysis of covariance (ANCOVA) for repeated measures was conducted to adjust for the potential confounding effects of socio-demographic (i.e., gender and age) and clinical characteristics (i.e., multi-vessel disease, cardiac history, hypertension, diabetes mellitus, family history of CAD, self-reported smoking, body mass index (BMI), and prescribed cardiac discharge medications (i.e., ACE-inhibitors, beta-blockers, calcium-antagonists, diuretics, oral nitrates, and statins)). Covariates were selected a priori based on the literature [1, 7].

In the current study, 19.3% (153/791) of patients was treated with PCI because of MI, 34.0% (269/791) due to UAP, and 46.6% (369/791) due to SAP. Mean anxiety and depression scores stratified by indication for PCI are shown in Figure 1. ANOVA for repeated measures showed that patients treated with PCI due to MI, UAP, or SAP did not differ significantly on anxiety ($F_{2\text{-}783}$=.85, p=.43) and depression ($F_{2\text{-}788}$=.67, p=.51) levels. The interaction effect of indication for PCI by time ($F_{2\text{-}783}$=.35, p=.71 for anxiety and $F_{2\text{-}788}$=.35, p=.71 for depression levels, respectively) and the main effect of time ($F_{1\text{-}783}$=.04, p=.84 for anxiety and $F_{1\text{-}788}$=.04, p=.84 for depression levels, respectively) were also not significant. This indicates that the anxiety and depression levels were generally stable over time, and independent of indication for PCI. Our main results did not change in adjusted analyses (Table 1).

Figure 1. Mean anxiety and depression scores stratified by indication for PCI



MI = myocardial infarction; UAP = unstable angina pectoris; SAP = stable angina pectoris

Table 1. Indication for PCI and anxiety and depression levels

	Anxiety		***Depression***	
	F	***p***	**F**	***p***
ANOVA for repeated measures				
Indication for PCI [a]	.85	.43	.67	.51
Time	.04	.84	.04	.84
Indication for PCI * Time	.35	.71	.35	.71
ANCOVA for repeated measures				
Indication for PCI [a]	.55	.58	.65	.52
Indication for PCI * Time	.93	.39	.53	.59
Male gender	9.00	.003**	.80	.37
Age	18.77	<.001***	.01	.92
Multi-vessel disease	.00	.98	.40	.53
Cardiac history [b]	1.12	.29	2.98	.085
Hypertension	2.23	.14	.25	.62
Diabetes mellitus	1.47	.23	1.88	.17
Family history of CAD	.02	.89	.94	.33
Self-reported smoking	.75	.39	4.41	.036*
BMI	3.79	.052	.00	.99
ACE-inhibitors	2.02	.16	.63	.43
Beta-blockers	.71	.40	4.18	.041*
Calcium-antagonists	.10	.76	2.43	.12
Diuretics	2.10	.15	4.68	.031*
Oral nitrates	1.04	.31	.43	.51
Statins	.02	.90	.02	.89

*$p \leq .05$; ** $p \leq .01$; *** $p \leq .001$

[a] Percutaneous coronary intervention (PCI) for myocardial infarction (MI), unstable angina pectoris (UAP), or stable angina pectoris (SAP)

[b] Previous MI, PCI, or coronary artery bypass graft (CABG) surgery

ACE = angiotensin-converting enzyme, BMI = body mass index (kg/m^2), CAD = coronary artery disease

The current study showed that indication for PCI was not systematically associated with anxiety and depression, which is in line with the findings from previous studies in ACS [6,8] and ICD [9] patients. Although one study demonstrated that ACS patients presenting with UAP had a significantly poorer HRQOL 7 months after their index-hospitalization as compared to patients presenting with MI [6], our study results did not corroborate this finding. This discrepancy may be explained by the focus on HRQOL rather than anxiety/depression, and the focus on ACS patients.

Although we expected MI patients undergoing PCI to experience higher levels of anxiety and depression than UAP or SAP patients, the current study did not confirm this hypothesis. It is plausible that especially psychological factors related to the subjective experience of the cardiac event are predictive of psychological distress in the long-term rather than objective measures of disease severity [8]. Previous studies have identified several psychological correlates of anxiety and depression in CAD, including the distressed (Type D) personality (i.e., the combination of negative affectivity and social inhibition traits) [11,13] and acute distress and fear of dying [8]. Given that anxiety and depression are associated with adverse clinical and patient-reported outcomes in CAD patients [4,5] and tend to be stable over time [10,11], it is recommended that future research and clinical practice focus on the early identification of patients at high-risk for psychological distress and look beyond factors related to disease severity and treatment.

Limitations of the current study should be acknowledged. First, no information on left ventricular ejection fraction was collected, which is an important risk factor for poor prognosis in CAD [4]. Second, no information on participation in cardiac rehabilitation and prescription of psychotropic medication was collected. Third, 31.5% of patients completing the HADS at baseline did not complete the HADS at 12 months. Possibly, a sampling bias occurred with those patients scoring higher on anxiety or depression being more likely to drop-out, as has been found in other studies [14]. Finally, as anxiety and depression levels were only assessed at 2 time points, mixed modelling was not feasible on our data.

In conclusion, in the current study patients treated with PCI for MI, UAP, or SAP did not differ in their anxiety and depression levels. Future research and clinical practice should focus on the early identification of patients at high-risk for psychological distress, and look beyond factors related to disease severity and treatment.

ACKNOWLEDGEMENTS

This research was in part supported with a VIDI grant (91710393) to Prof. Susanne S. Pedersen from the Netherlands Organization for Health Research and Development (ZonMW), The Hague, the Netherlands. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [15].

REFERENCES

1. Hirsch A, Verouden NJW, Koch KT, Baan J, Henriques JPS, Piek JJ, et al. Comparison of long-term mortality after percutaneous coronary intervention in patients treated for acute ST-elevation myocardial infarction versus those with unstable and stable angina pectoris. Am J Cardiol. 2009;104(3):333-7.
2. de Feyter PJ, Serruys PW, Unger F, Beyar R, de Valk V, Milo S, et al. Bypass surgery versus stenting for the treatment of multivessel disease in patients with unstable angina compared with stable angina. Circulation. 2002;105(20):2367-72.
3. Connerney I, Sloan RP, Shapiro PA, Bagiella E, Seckman C. Depression is associated with increased mortality 10 years after coronary artery bypass surgery. Psychosom Med. 2010;72(9):874-81.
4. Strik JJMH, Denollet J, Lousberg R, Honig A. Comparing symptoms of depression and anxiety as predictors of cardiac events and increased health care consumption after myocardial infarction. J Am Coll Cardiol. 2003;42(10):1801-7.
5. Lane D, Carroll D, Ring C, Beevers DG, Lip GYH. Mortality and quality of life 12 months after myocardial infarction: Effects of depression and anxiety. Psychosom Med. 2001;63(2):221-30.
6. Rumsfeld JS, Magid DJ, Plomondon ME, O'Brien MM, Spertus JA, Every NR, et al. Predictors of quality of life following acute coronary syndromes. Am J Cardiol. 2001;88(7):781-4.
7. Maddox T, Reid K, Rumsfeld J, Spertus J. One-year health status outcomes of unstable angina versus myocardial infarction: A prospective, observational cohort study of ACS survivors. BMC Cardiovasc Disord. 2007;7(1):28.
8. Whitehead DL, Strike P, Perkins-Porras L, Steptoe A. Frequency of distress and fear of dying during acute coronary syndromes and consequences for adaptation. Am J Cardiol. 2005;96(11):1512-6.
9. Pedersen SS, Sears SF, Burg MM, van den Broek KC. Does ICD indication affect quality of life and levels of distress? Pacing Clin Electrophysiol. 2009;32(2):153-6.
10. Damen NL, Pelle AJ, van Geuns RM, van Domburg RT, Boersma E, Pedersen SS. Intra-individual changes in anxiety and depression during 12-month follow-up in percutaneous coronary intervention patients. J Affect Disord. 2011;134(1–3):464-7.
11. van Gestel YRBM, Pedersen SS, van de Sande M, de Jaegere PPT, Serruys PW, Erdman RAM, et al. Type-D personality and depressive symptoms predict anxiety 12 months post-percutaneous coronary intervention. J Affect Disord. 2007;103(1):197-203.
12. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med. 1997;27(2):363-70.
13. Pedersen SS, van Domburg RT, Theuns DAMJ, Jordaens L, Erdman RAM. Type D personality is associated with increased anxiety and depressive symptoms in patients with an implantable cardioverter defibrillator and their partners. Psychosom Med. 2004;66(5):714-9.
14. McGrady A, McGinnis R, Badenhop D, Bentle M, Rajput M. Effects of depression and anxiety on adherence to cardiac rehabilitation. J Cardiopulm Rehabil Prev. 2009;29(6):358-64.
15. Shewan LG, Coats AJS. Adherence to ethical standards in publishing scientific articles: A statement from the International Journal of Cardiology. Int J Cardiol. 2012;161(3):124-5.

CHAPTER 3

Intra-individual changes in anxiety and depression during 12-month follow-up in percutaneous coronary intervention patients

Damen NL, Pelle AJ, van Geuns RM, van Domburg RT, Boersma E, Pedersen SS. J Affect Disord. 2011;134(1–3):464-7.
Short report

ABSTRACT

Background: Only a paucity of studies focused on intra-individual changes in anxiety and depression over time and its correlates in cardiac patients, which may contribute to the identification of high-risk patients and point to targets for intervention. We examined changes in anxiety and depression over a 12-month period and the socio-demographic and clinical correlates of change scores using an intra-individual approach in patients treated with percutaneous coronary intervention (PCI).

Methods: Consecutive PCI patients (N=715) completed the Hospital Anxiety and Depression Scale (HADS) at baseline and 12 months post-PCI. Individual change scores were calculated and in secondary analyses, 3 categories of change were identified (i.e., stable, improved, and deteriorated anxiety or depression).

Results: The mean individual change was -.16 (±3.0) for anxiety and -.02 (±2.8) for depression. In linear regression analyses, baseline anxiety levels (B=-.25, 95%CI [-.30 - -.20], $p<.001$) and baseline depression levels (B=-.28, 95%CI [-.33 - -.22], $p<.001$) were significant correlates of individual change scores. Secondary analyses showed that anxiety remained stable in 76.4% (546/715) of patients, while depression remained stable in 81.4% (582/715) of patients.

Conclusions: The findings of the current study showed that levels of anxiety and depression remained stable in the majority of PCI patients from the index-PCI to 12 months post-PCI. Future studies using an intra-individual approach are warranted to further examine individual changes in anxiety and depression over time in CAD, and PCI in particular, as a means to bridge the gap between research and clinical practice.

INTRODUCTION

Anxiety and depression are common in patients with established coronary artery disease (CAD) [1], with prevalence rates ranging from 20-50% for anxiety [2, 3] and 30-60% for depression [4-6], respectively. Both anxiety and depression have been associated with increased cardiovascular morbidity and mortality [7-9], increased health care consumption [2, 3], and impaired health-related quality of life [10]. Generally, anxiety and depression in CAD have been examined by means of incidence and prevalence rates [2, 9], or changes in overall mean scores over time [11, 12]. However, these approaches mask intra-individual changes over time and, consequently, potential differential risks of adverse health outcomes may be overlooked [7, 12-14].

Given that anxiety and depression are associated with poor prognosis in CAD [7-9], knowledge of the correlates of changes in anxiety and depression may contribute to the identification of high-risk patients [15] and point to targets for intervention [16]. Only a paucity of studies have focused on intra-individual changes in anxiety and depression over time and its correlates in cardiac patients using different statistical approaches, with these studies focusing on implantable cardioverter defibrillator (ICD) patients [17, 18], post-myocardial infarction (MI) patients [7, 14], patients admitted for elective coronary artery bypass grafting (CABG) surgery [9, 12, 14], and a specific subsample of exhausted patients treated with percutaneous coronary intervention (PCI) [15]. Hence, the aims of the current study in patients treated with PCI were to 1) examine changes in anxiety and depression over time using an intra-individual approach, and 2) examine the socio-demographic and clinical correlates of changes in anxiety and depression over a 12-month period.

METHODS

Our sample comprised 715 consecutive patients (75.8% men; mean age 63.6±10.8 years, range [30-87] years) treated with PCI at the Erasmus MC, Rotterdam, the Netherlands. The Dutch version of the 14-item Hospital Anxiety and Depression Scale (HADS) was used to assess levels of anxiety and depression at baseline (i.e., 4 weeks post PCI) and at 12 months post-PCI [19]. The HADS anxiety and depression subscale scores range from 0 to 21, with a higher score indicating higher levels of distress. Given the 2 time points, individual change scores were calculated using the absolute difference between levels of anxiety and depression at baseline and 12-month follow-up. Linear regression analyses were used to examine correlates of these individual change scores. A priori, we decided to enter gender, age, indication for PCI (stable angina/unstable angina vs. myocardial infarction (MI)), multi-vessel disease (multi-vessel disease vs. single-vessel disease/no vessel disease), cardiac history (previous MI, PCI, or CABG surgery), and CAD risk factors

(hypertension, hypercholesterolemia, family history of CAD, self-reported smoking, and diabetes mellitus) as potential correlates of change based on the literature [15, 16]. Moreover, in order to correct for regression to the mean, we adjusted for baseline levels of anxiety and depression [20]. Prescribed cardiac medications were not considered, as there is no evidence to suggest that they have an influence on anxiety and depression scores.

In secondary analyses, established cut-off scores of the HADS (i.e., scores ranging from 0 to 7 indicating normal levels, scores ranging from 8 to 11 indicating mild to moderate levels, and scores ≥12 indicating severe levels of anxiety and depression) were used to identify 3 categories of change in anxiety and depression (i.e., stable, improved, and deteriorated) [21]. Using logistic regression analyses, we focused on correlates of deteriorated anxiety and depression using stable/improved as the reference category.

The study protocol was approved by the medical ethics committee of the participating hospital and conducted according to the Helsinki declaration [22]. Patients participated on a voluntary basis, and were able to withdraw from the study at any moment, without this decision having implications for future medical treatment. Every patient provided informed consent.

RESULTS

The mean anxiety and depression scores at baseline for the total sample were 5.3 (±3.7) and 4.4 (±3.8), while 12-month mean scores were 5.1 (±4.0) and 4.4 (±3.8). The mean individual change in anxiety scores was -.16 (±3.0), while the mean individual change in depression scores was -.02 (±2.8). Overall, univariable and multivariable analyses yielded similar results. In multivariable linear regression analyses, only baseline anxiety levels (B=-.25 95%CI [-.30 - -.20], p<.001) and baseline depression levels (B=-.28, 95%CI [-.33 - -.22], p<.001) were significantly associated with individual change scores in anxiety and depression over the 12-month follow-up period (Table 1), with higher baseline levels associated with less of a change in anxiety and depression scores over time.

As listed in Tables 2a and 2b, anxiety remained stable in 76.4% (546/715) of patients, while depression remained stable in 81.4% (582/715) of patients. Anxiety improved in 10.9% (78/715) of patients and in 12.7% (91/715) of patients anxiety deteriorated. In 9.0% (64/715) of patients depression improved and in 9.7% (69/715) of patients depression deteriorated. In multivariable logistic regression analyses, baseline levels of anxiety were highly associated with deteriorations in anxiety (OR=1.11, 95%CI [1.04-1.18], p=.001), as were baseline levels of depression (OR=1.09, 95%CI [1.03-1.16], p=.005) (Table 1).

Table 1. Correlates of individual changes in anxiety and depression scores during the 12-month follow-up period (multivariable regression analyses)

	Linear regression analyses					
	Individual change scores for anxiety			Individual change scores for depression		
	B	**95% CI**	***p***	**B**	**95% CI**	***p***
Male gender	-.12	-.61-.36	.61	-.28	-.73-.18	.23
Age	-.00	-.01-.00	.41	.00	-.00-.01	.60
MI	.27	-.39-.94	.42	.16	-.47-.79	.62
Cardiac history [a]	-.11	-.55-.33	.62	-.23	-.65-.19	.27
Multi-vessel disease	-.17	-.61-.27	.44	.06	-.35-.48	.77
Family history of CAD	-.16	-.59-.27	.46	.01	-.40-.42	.96
Self-reported smoking	-.11	-.64-.42	.69	.07	-.40-.52	.78
Hypercholesterolemia	-.51	-1.05-.03	.062	.05	-.43-.56	.85
Hypertension	-.00	-.44-.44	1.00	.26	-.46-.67	.22
Diabetes mellitus	-.09	-.65-.47	.75	.19	-.16-.71	.49
Baseline levels	-.24	-.30- -.19	<.001**	-.27	-.34- -.22	<.001**

Table 1. *Continued*

	Logistic regression analyses					
	Deteriorated anxiety			Deteriorated depression		
	OR	**95% CI**	***p***	**OR**	**95% CI**	***p***
Male gender	.78	.46-1.34	.37	.94	.50-1.76	.85
Age	.99	.97-1.02	.56	.99	.97-1.02	.57
MI	1.00	.50-2.03	.99	.29	.09-.99	.058
Cardiac history [a]	.85	.52-1.40	.52	.89	.51-1.55	.68
Multi-vessel disease	.75	.46-1.22	.24	.84	.48-1.47	.55
Family history of CAD	1.12	.69-1.79	.65	1.10	.64-1.87	.74
Self-reported smoking	1.08	.59-1.98	.81	1.00	.48-2.06	.99
Hypercholesterolemia	.65	.36-1.17	.15	.87	.44-1.74	.70
Hypertension	.86	.53-1.42	.56	.78	.44-1.37	.38
Diabetes mellitus	.69	.34-1.40	.31	1.09	.54-2.20	.82
Baseline levels	1.11	1.05-1.18	.001***	1.09	1.03-1.16	.005**

*$p \leq .05$; ** $p \leq .01$; *** $p \leq .001$

[a] Previous myocardial infarction (MI), percutaneous coronary interventions (PCI), or coronary artery bypass graft (CABG) surgery

CAD = coronary artery disease

Table 2a. Stability of anxiety over time during the 12-month follow-up period [a]

		Baseline levels of anxiety [b]		
		Normal levels	**Mild to moderate levels**	**Severe levels**
12-month levels of anxiety [b]	**Normal levels**	470 (65.7)[c]	53 (7.4)[d]	13 (1.8)[d]
	Mild to moderate levels	57 (8.0)[e]	53 (7.4)[c]	12 (1.7)[d]
	Severe levels	12 (1.7)[e]	22 (3.1)[e]	23 (3.1)[c]

[a] Results are presented as n (%) unless otherwise stated.
[b] Levels of anxiety were based on established cut-off scores of the HADS, with scores ranging from 0 to 7 indicating normal levels, scores ranging from 8 to 11 indicating mild to moderate levels, and scores ≥12 indicating severe levels of anxiety [21]
[c] Stable anxiety: 546/715= 76.4%
[d] Improved anxiety: 78/715= 10.9%
[e] Deteriorated anxiety: 91/715= 12.7%

Table 2b. Stability of depression over time during the 12-month follow-up period [a]

		Baseline levels of depression [b]		
		Normal levels	**Mild to moderate levels**	**Severe levels**
12-month levels of depression [b]	**Normal levels**	512 (71.6)[c]	41 (5.7)[d]	5 (0.7)[d]
	Mild to moderate levels	49 (6.9)[e]	55 (7.7)[c]	18 (2.5)[d]
	Severe levels	7 (1.0)[e]	13 (1.8)[e]	15 (2.1)[c]

[a] Results are presented as n (%) unless otherwise stated.
[b] Levels of depression were based on established cut-off scores of the HADS, with scores ranging from 0 to 7 indicating normal levels, scores ranging from 8 to 11 indicating mild to moderate levels, and scores ≥12 indicating severe levels of depression [21]
[c] Stable depression: 582/715= 81.4%
[d] Improved depression: 64/715= 9.0%
[e] Deteriorated depression: 69/715= 9.7%

DISCUSSION

Our study demonstrated that the majority of patients did not experience significant changes in levels of anxiety and depression from the index-PCI to 12-month follow-up (i.e., 76.4% for anxiety and 81.4% for depression, respectively). A stable pattern of anxiety and depression was demonstrated previously in ICD patients [17, 18], post-MI patients [7], patients admitted for elective CABG surgery [9], and exhausted PCI patients [15]. In the current study, anxiety deteriorated in 12.7% of patients, whereas in 9.7% of patients depression deteriorated, which is in line with previous studies [9, 23].

Baseline levels of anxiety and depression were associated with psychological distress levels over time, indicating that the higher the baseline levels, the lower the change in anxiety and depression scores over time. In contrast to previous studies, in the current study none of the included socio-demographic and clinical variables were associated with individual changes in anxiety and depression [12, 14, 15]. However, these previous studies did not focus on intra-individual changes over time, with the possibility that correlates of mean scores and trajectories may be different than correlates of change scores. Future studies are warranted to further examine intra-individual changes in anxiety and depression over time and its correlates in the context of CAD, and PCI in particular, since clinically relevant intra-individual change standards and knowledge of the correlates of change may contribute to the identification of high-risk patients and provide targets for interventions [13, 18].

Strengths of the study include the novel approach of examining intra-individual changes in anxiety and depression rather than focusing on between-group differences over time, the relatively large sample size, and the use of a validated and standardized questionnaire to assess levels of anxiety and depression [19]. However, some limitations must be acknowledged. First, subclinical levels of anxiety and depression were assessed using self-reports rather than a clinical diagnostic interview. Second, 31% of patients completing the HADS at baseline did not complete the HADS at 12 months. Possibly, a sampling bias occurred with those patients scoring higher on depression being more likely to drop-out ($t(1035) = -2.71$, 95%CI [-1.21- -.19], $p = .01$). Finally, information on history of anxiety and depression, participation in cardiac rehabilitation, and use of psychotropic medication was not collected, and therefore, we were not able to control statistically for these variables in multivariable analyses.

In conclusion, the findings of the current study showed that levels of anxiety and depression remained stable in the majority of PCI patients from the index-PCI to 12 months post-PCI. Future studies using an intra-individual approach are warranted to further examine individual changes in anxiety and depression over time and the potential implications for morbidity and mortality in CAD, and PCI in particular, as a means to bridge the gap between research and clinical practice.

ROLE OF THE FUNDING SOURCE

The current study was funded by a VICI-grant from the Netherlands Organization for Scientific Research (NWO) to J. Denollet (#453-04-004). The NWO had no further role in study design, collection, analysis and interpretation of the data, writing of the report, and the decision to submit the paper for publication.

CONFLICT OF INTEREST

None declared.

ACKNOWLEDGEMENTS

This research was in part supported with a VIDI grant (91710393) to Dr. Susanne S. Pedersen from the Netherlands Organization for Health Research and Development (ZonMw), The Hague, the Netherlands.

REFERENCES

1. Moser DK, Dracup K, Evangelista LS, Zambroski CH, Lennie TA, Chung ML, et al. Comparison of prevalence of symptoms of depression, anxiety, and hostility in elderly patients with heart failure, myocardial infarction, and a coronary artery bypass graft. Heart Lung J Acute Crit Care. 2010;39(5):378-85.
2. Grace SL, Abbey SE, Irvine J, Shnek ZM, Stewart DE. Prospective examination of anxiety persistence and its relationship to cardiac symptoms and recurrent cardiac events. Psychother Psychosom. 2004;73(6):344-52.
3. Strik JJMH, Denollet J, Lousberg R, Honig A. Comparing symptoms of depression and anxiety as predictors of cardiac events and increased health care consumption after myocardial infarction. J Am Coll Cardiol. 2003;42(10):1801-7.
4. Thombs BD, Bass EB, Ford DE, Stewart KJ, Tsilidis KK, Patel U, et al. Prevalence of depression in survivors of acute myocardial infarction. J Gen Intern Med. 2006;21(1):30-8.
5. Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease: Epidemiology, biology, and treatment. Arch Gen Psychiatry. 1998;55(7):580-92.
6. Barefoot JC, Burg MM, Carney RM, Cornell CE, Czajkowski SM, Freedland KE, et al. Aspects of social support associated with depression at hospitalization and follow-up assessment among cardiac patients. J Cardiopulm Rehabil. 2003;23(6):404-12.
7. Kaptein KI, de Jonge P, van den Brink RHS, Korf J. Course of depressive symptoms after myocardial infarction and cardiac prognosis: A latent class analysis. Psychosom Med. 2006;68(5):662-8.
8. Frasure-Smith N, Lesperance F, Gravel G, Masson A, Juneau M, Talajic M, et al. Social support, depression, and mortality during the first year after myocardial infarction. Circulation. 2000;101(16):1919-24.
9. Blumenthal JA, Lett HS, Babyak MA, White W, Smith PK, Mark DB, et al. Depression as a risk factor for mortality after coronary artery bypass surgery. Lancet. 2003;362(9384):604-9.
10. Lane D, Carroll D, Ring C, Beevers DG, Lip GYH. Mortality and quality of life 12 months after myocardial infarction: Effects of depression and anxiety. Psychosom Med. 2001;63(2):221-30.
11. van Gestel YRBM, Pedersen SS, van de Sande M, de Jaegere PPT, Serruys PW, Erdman RAM, et al. Type-D personality and depressive symptoms predict anxiety 12 months post-percutaneous coronary intervention. J Affect Disord. 2007;103(1):197-203.
12. Duits AA, Duivenvoorden HJ, Boeke S, Taams MA, Mochtar B, Krauss XH, et al. The course of anxiety and depression in patients undergoing coronary artery bypass graft surgery. J Psychosom Res. 1998;45(2):127-38.
13. Hawkes AL, Mortensen OS. Up to one third of individual cardiac patients have a decline in quality of life post-intervention. Scand Cardiovasc J. 2006;40(4):214-8.
14. Murphy BM, Elliott PC, Worcester MUC, Higgins RO, Le Grande MR, Roberts SB, et al. Trajectories and predictors of anxiety and depression in women during the 12 months following an acute cardiac event. Br J Health Psychol. 2008;13(1):135-53.
15. Pedersen SS, Smith ORF, de Vries J, Appels A, Denollet J. Course of anxiety symptoms over an 18-month period in exhausted patients post percutaneous coronary intervention. Psychosom Med. 2008;70(3):349-55.
16. Spindler H, Pedersen SS, Serruys PW, Erdman RA, van Domburg RT. Type-D personality predicts chronic anxiety following percutaneous coronary intervention in the drug-eluting stent era. J Affect Disord. 2007;99(1-3):173-9.
17. Pedersen SS, van den Broek KC, Theuns DA, Erdman RA, Alings M, Meijer A, et al. Risk of chronic anxiety in implantable defibrillator patients: A multi-center study. Int J Cardiol. 2009;147(3):420-3.
18. Pedersen SS, Theuns DAMJ, Jordaens L, Kupper N. Course of anxiety and device-related concerns in implantable cardioverter defibrillator patients the first year post implantation. Europace. 2010;12(8):1119-26.

19. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med. 1997;27(2):363-70.
20. Twisk JWR. Applied longitudinal data analysis for epidemiology: A practical guide. Cambridge University Press; 2003.
21. Snaith RP. The Hospital Anxiety and Depression Scale. Health Qual Life Outcomes. 2003;1(1):29.
22. Goodyear MDE, Krleza-Jeric K, Lemmens T. The declaration of Helsinki. Br Med J. 2007;335(7621):624-5.
23. Murphy BM, Elliott PC, Higgins RO, Le Grande MR, Worcester MUC, Goble AJ, et al. Anxiety and depression after coronary artery bypass graft surgery: Most get better, some get worse. Eur J Cardiovasc Prev Rehabil. 2008;15(4):434-40.

CHAPTER 4

Depression is independently associated with 7-year mortality in patients treated with percutaneous coronary intervention: Results from the RESEARCH registry

Damen NL, Versteeg H, Boersma E, Serruys PW, Van Geuns RM, Denollet J, van Domburg RT, Pedersen SS. Int J Cardiol. 2013;167(6):2496-501.

ABSTRACT

Background: Depression has been associated with poor prognosis in patients with coronary artery disease (CAD), but little is known about the impact of depression on long-term mortality. We examined whether depression was associated with 7-year mortality in patients treated with percutaneous coronary intervention (PCI), after adjusting for socio-demographic and clinical characteristics, anxiety, and the distressed (Type D) personality.

Methods: The sample comprised a cohort of consecutive PCI patients (N=1234; 72.0% men; mean age 62.0±11.1 years, range [26-90] years) from the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry. At baseline (i.e., 6 months post-PCI), patients completed the Hospital Anxiety and Depression Scale (HADS) to assess anxiety and depression and the Type D scale (DS14) to assess Type D personality. The endpoint was defined as all-cause mortality.

Results: The prevalence of depression (HADS-D≥8) was 26.2% (324/1236). After a median follow-up of 7.0±1.6 years, 187 deaths (15.2%) from any cause were recorded. The incidence of all-cause mortality in depressed patients was 23.5% (76/324) versus 12.2% (111/910) in non-depressed patients. Cumulative hazard functions differed significantly for depressed versus non-depressed patients (log-rank X^2=25.57, p<.001). In multivariable analysis, depression remained independently associated with all-cause mortality (HR=1.63; 95%CI [1.05-2.71], p=.038), after adjusting for socio-demographic and clinical characteristics, anxiety, and Type D personality.

Conclusions: Depression was independently associated with a 1.6-fold increased risk for 7-year mortality, above and beyond anxiety and Type D personality. Future studies are warranted to further elucidate the potential pathways linking depression to long-term mortality following PCI.

INTRODUCTION

Depression is common in patients with coronary artery disease (CAD), with prevalence rates ranging between 25-50% [1-5]. Depression is associated with an increased risk for all-cause and cardiac mortality, independent of disease severity [6-9]. Previous studies with follow-up durations ranging from 1 to 3.5 years have shown that depressed patients had a 1.2 to 3.7-fold increased risk for death as compared with non-depressed patients after myocardial infarction (MI) [1, 6, 8, 10-13]. These findings were replicated in samples of patients who underwent coronary artery bypass graft (CABG) surgery [2, 14] or percutaneous coronary intervention (PCI) [9], and in heart failure patients [3, 7]. Recent meta-analyses have confirmed the prognostic association between depression and mortality in cardiac patients [15-18].

As depression tends to be stable over time [14, 19, 20], it is possible that depression is also predictive of long-term mortality (≥5 years). To date, only a paucity of studies in post-MI patients [4, 21], CABG patients [5, 14], and patients referred for exercise testing [22] have examined the impact of depression on long-term mortality. In 3 of these studies, a significant association between depression and long-term mortality was found [5, 14, 21], whereas in 2 other studies depression was associated with short-term but not long-term prognosis [4, 22].

In the context of CAD, there has been a tendency to focus on one risk factor at a time, which has also been labeled as the 'risk factor of the month approach' [23, 24]. The question remains whether depression exerts an independent effect on prognosis or whether other psychological risk factors, like anxiety and the distressed (Type D) personality (i.e., the combined tendency to experience negative emotions and to inhibit self-expression [25]), may explain some of the variance in the association between depression and mortality.

Hence, the aim of the current study was to examine whether depression is associated with 7-year mortality in patients treated with PCI, after adjusting for socio-demographic and clinical characteristics, anxiety, and Type D personality.

METHODS

Participants and procedure

The study sample comprised a cohort of consecutive CAD patients treated with PCI, with either sirolimus-eluting stenting (SES) or bare-metal stenting (BMS), between September 2, 2001 and November 14, 2002 at the Erasmus MC, Rotterdam, the Netherlands, as part of the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry. The design of the RESEARCH registry has been published previously [26, 27]. In brief, the registry was designed to evaluate the efficacy and safety of SES implantation in the

"real world" of interventional cardiology. Hence, no exclusion criteria were applied for patients entering the registry, and all PCI patients were eligible for enrolment regardless of anatomical or clinical presentation [26].

At 6 months post-PCI (referred to as baseline in the remainder of the paper), all living patients were asked to complete a set of standardized and validated psychological questionnaires. Due to logistic reasons and in accordance with previous studies on long-term clinical outcomes in PCI patients, assessment at 6 months was chosen so as to represent patients in a stable condition, as the risk for restenosis is increased in the 0-6 month period post-PCI [28]. All patients were prospectively followed for adverse clinical events. The study protocol was approved a priori by the medical ethics committee of the Erasmus MC, Rotterdam, and the study was conducted according to the Helsinki Declaration [29]. Every patient provided informed consent.

Measures

Socio-demographic and clinical characteristics

Socio-demographic characteristics included gender and age. Clinical characteristics included type of stent (BMS vs. SES implantation), multi-vessel disease (multi-vessel disease vs. single-vessel disease/no vessel disease), body mass index (BMI), cardiac history (i.e., previous MI, CABG surgery, or PCI), indication for PCI (stable angina/silent ischemia, unstable angina, or MI), renal failure (i.e., glomular filtration rate (GFR) <15) [30], CAD risk factors (i.e., hypertension, hypercholesterolemia, diabetes mellitus, family history of CAD, and self-reported smoking), and prescribed cardiac discharge medications (i.e., aspirin, ACE-inhibitors, beta-blockers, calcium-antagonists, diuretics, oral nitrates, and statins). Information on clinical variables was prospectively collected at the time of the index-PCI/ baseline and recorded in the institutional database.

Anxiety and depression

Patients completed the Dutch version of the Hospital Anxiety and Depression Scale (HADS) at baseline to assess symptoms of anxiety and depression [31, 32]. Both subscales consist of 7 items that are answered on a 4-point Likert scale ranging from 0 to 3 [31]. A cut-off score ≥8 on each subscale represents clinically relevant levels of anxiety and depression [33]. The HADS has demonstrated to be a valid screening tool for detecting symptoms of anxiety and depression [33, 34] and has been shown to predict mortality in patients referred for exercise testing [22]. The internal consistency has been demonstrated previously with Cronbach's alpha of .83 for the anxiety subscale (HADS-A) and .82 for the depression subscale (HADS-D) [33]. In the current study, the correlation between both subscales was .69 and Cronbach's alpha was .85 for both HADS-A and HADS-D.

Type D personality

At baseline, Type D personality was assessed with the 14-item Type D scale (DS14) that comprises 2 subscales, negative affectivity (e.g., "I often feel unhappy") and social inhibition (e.g., "I am a closed kind of person"), each consisting of 7 items. Items are scored on a 5-point Likert scale ranging from 0 ("false") to 4 ("true"). Based on findings from the Item Response Theory [35], a standardized cut-off score ≥10 on both subscales is used to identify individuals with a Type D personality. Previous research suggested that the co-occurrence of negative affectivity and social inhibition, rather than the single traits, predicts adverse events in PCI patients [36]. Assessment of Type D with the DS14 is internally consistent [37], not confounded by disease severity [38, 39], and relatively stable over time [38, 39].

Endpoint

The endpoint was defined as all-cause mortality. Deaths (n=54) occurring between PCI and psychological assessment were excluded as an endpoint from the analyses. Information on survival status was obtained from the Municipal Civil Registries in May 2009. The median follow-up period for all-cause mortality was 7.0±1.6 years (range [.7-8.6] years). Survival status at follow-up was known for all patients (100%). Information on cause of death was requested from the Central Bureau of Statistics (CBS) of the Netherlands and was divided into cardiac death (i.e., death due to arrhythmias, myocardial infarction, heart failure, or sudden cardiac death) and non-cardiac death (i.e., death due to cancer or other causes).

Statistical analyses

Group differences between depressed and non-depressed patients were examined using the Chi-square test for nominal variables and Student's t-test for independent samples for continuous variables. Cumulative survival curves for depression (i.e., absent versus present, cut-off score ≥8) were constructed using the Kaplan-Meier method. The log-rank test was used to compare cumulative survival curves between groups. Univariable and multivariable Cox regression models were used to examine the effect of depression on all-cause mortality. Covariates were entered into the model using the Enter method, thereby reducing the risk of overfitting [40]. In multivariable analysis, we adjusted for socio-demographic characteristics (i.e., gender and age), clinical characteristics (i.e., type of stent, multi-vessel disease, cardiac history, indication for PCI, renal failure, hypertension, hypercholesterolemia, diabetes mellitus, family history of CAD, self-reported smoking, BMI, and prescribed cardiac medications), anxiety, and Type D personality. Covariates were selected a priori based on the literature [1, 5, 9, 41, 42]. Since almost all patients (i.e., 95%) were prescribed aspirin, we did not add aspirin as a covariate to the multivariable model.

In addition, a multivariable Cox regression model was conducted to examine whether continuous depression scores were associated with all-cause mortality. Further, a univariable Cox regression model was conducted to examine the relationship between depression and cardiac mortality in addition to all-cause mortality.

Hazard Ratios (HRs) with their corresponding 95% CIs were reported for Cox regression analyses. All results were based on 2-tailed tests and a *p*-value <.05 was used to indicate statistical significance. All statistical analyses were performed using SPSS for Windows 17.0 (SPSS Inc., Chicago, Illinois, USA).

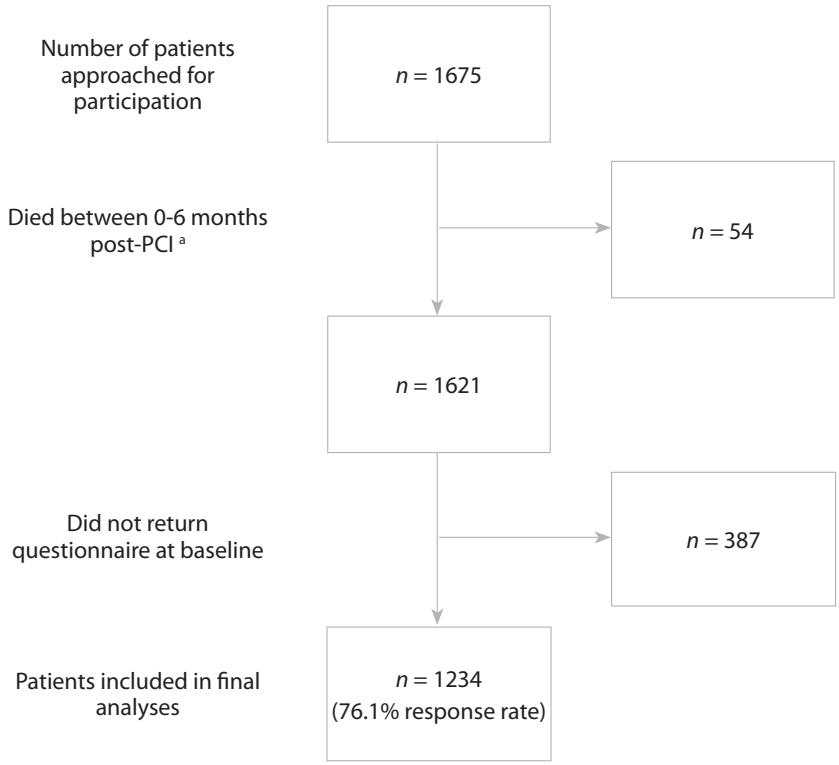
RESULTS

Patient characteristics

Of 1675 eligible patients treated with PCI in the study period, 54 died within 6 months. The remaining 1621 patients were asked to participate in the study, of which 387 did not return the questionnaire at baseline (76.1% response rate). Thus, final analyses were based on data from 1234 patients (72.0% men; mean age 62.0±11.1 years, range [26-90] years). In Figure 1, a flowchart of the patient selection is provided. No systematic differences between participants (N=1234) and non-participants (n=387) were found, except for non-participants more often having diabetes mellitus as compared with participants (21.0% vs. 15.0%, $p<.05$).

The prevalence of depression was 26.3% (324/1234). At follow-up, 187 deaths (15.2%) from any cause were recorded. Patient characteristics stratified by depression are presented in Table 1. Depressed and non-depressed patients differed on some baseline characteristics, with depressed patients more often being female, older, having a cardiac history, diabetes mellitus, and anxiety, but less often having a family history of CAD and being prescribed statins.

Figure 1. Flowchart of patient selection



[a] before questionnaire completion at baseline

Table 1. Patient characteristics for the total sample and stratified by depression [a]

	Total sample (N=1234)	***Depression (n=324)***	***No depression (n=910)***	***p***
Socio-demographic characteristics				
Male gender	888 (72.0)	203 (62.7)	685 (75.3)	<.001***
Age, mean (SD)	62.0 (11.1)	63.4 (11.7)	61.5 (10.9)	.012*
Clinical characteristics				
Sirolimus-eluting stent	703 (57.0)	197 (60.8)	506 (55.6)	.12
Multi-vessel disease	666 (54.0)	190 (58.6)	476 (52.3)	.057
Cardiac history [b]	695 (57.3)	203 (64.2)	492 (54.9)	.005**
Indication for PCI				.27
Stable angina/ Silent ischemia	623 (50.7)	172 (53.4)	451 (49.7)	
Unstable angina	438 (35.6)	114 (35.4)	324 (35.7)	
MI	168 (13.7)	36 (11.2)	132 (14.6)	
Renal failure	42 (5.4)	11 (5.2)	31 (5.4)	1.00
Hypertension	513 (41.6)	150 (46.3)	363 (39.9)	.054
Hypercholesterolemia	997 (80.9)	259 (79.9)	738 (81.2)	.68
Diabetes Mellitus	185 (15.0)	67 (20.7)	118 (13.0)	.001***
Family history of CAD	358 (29.0)	78 (24.1)	280 (30.8)	.026*
Self-reported smoking	371 (30.1)	105 (32.4)	266 (29.3)	.32
BMI, mean (SD)	27.1 (5.2)	27.3 (5.3)	27.0 (5.2)	.50
Cardiac medication				
Aspirin	1162 (94.9)	301 (93.8)	861 (95.3)	.34
ACE-inhibitors	402 (32.8)	101 (31.5)	301 (33.3)	.59
Beta-blockers	815 (66.6)	201 (62.6)	614 (68.0)	.092
Calcium-antagonists	619 (50.6)	168 (52.3)	451 (49.9)	.50
Diuretics	184 (15.0)	59 (18.4)	125 (13.8)	.062
Oral nitrates	187 (15.3)	60 (18.7)	127 (14.1)	.059
Statins	894 (73.0)	211 (65.7)	683 (75.6)	.001***

Table 1. *Continued*

	Total sample (N=1234)	*Depression (n=324)*	*No depression (n=910)*	*p*
Psychological characteristics				
Anxiety (i.e., HADS-A ≥8)	359 (29.1)	236 (73.1)	123 (13.5)	<.001***
Type D personality	353 (29.2)	104 (32.5)	249 (28.0)	.15

*$p \leq .05$; ** $p \leq .01$; *** $p \leq .001$

[a] Results are presented as n (%) unless otherwise stated

[b] Previous myocardial infarction (MI), percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG) surgery

ACE = angiotensin-converting enzyme, BMI = body mass index (kg/m^2), CAD = coronary artery disease, HADS-A = Hospital Anxiety and Depression Scale - Anxiety

Symptoms of depression and all-cause mortality

The incidence of all-cause mortality at follow-up (median follow-up period 7.0±1.6 years, range [.7-8.6] years) in depressed patients was 23.5% (76/324) versus 12.2% (111/910) in non-depressed patients (Figure 2). Cumulative hazard functions differed significantly for depressed versus non-depressed patients (log-rank X^2=25.57, p<.001). In univariable Cox regression analysis, depression was associated with a cumulative increased risk for all-cause mortality (HR=2.09; 95%CI [1.56-2.80], p<.001) (Figure 3). In multivariable Cox regression analysis, depression remained independently associated with all-cause mortality (HR=1.63; 95%CI [1.05-2.71], p=.038), after adjusting for socio-demographic and clinical characteristics, anxiety, and Type D personality (Table 2). Male gender, older age, hypercholesterolemia, and diabetes mellitus were significantly associated with an increased risk for all-cause mortality as well, whereas the prescription of statins was associated with a reduced risk for all-cause mortality. No significant effects were found for anxiety and Type D personality in relation to the endpoint.

Additional analysis examining the impact of depression on all-cause mortality using a continuous score of depression yielded similar results as compared to the analysis using a dichotomized depression score (results not shown). Cause of death was known for a subset of patients (n=830). The incidence of cardiac mortality at follow-up in depressed patients was 7.6% (15/197) versus 4.9% (31/633) in non-depressed patients. In univariable Cox regression analysis, depression was not significantly related to cardiac mortality (HR=1.65; 95%CI [.89-3.06], p=.11), and therefore, we decided not to perform additional multivariable analysis.

Figure 2. Proportion of all-cause mortality at follow-up stratified by depression

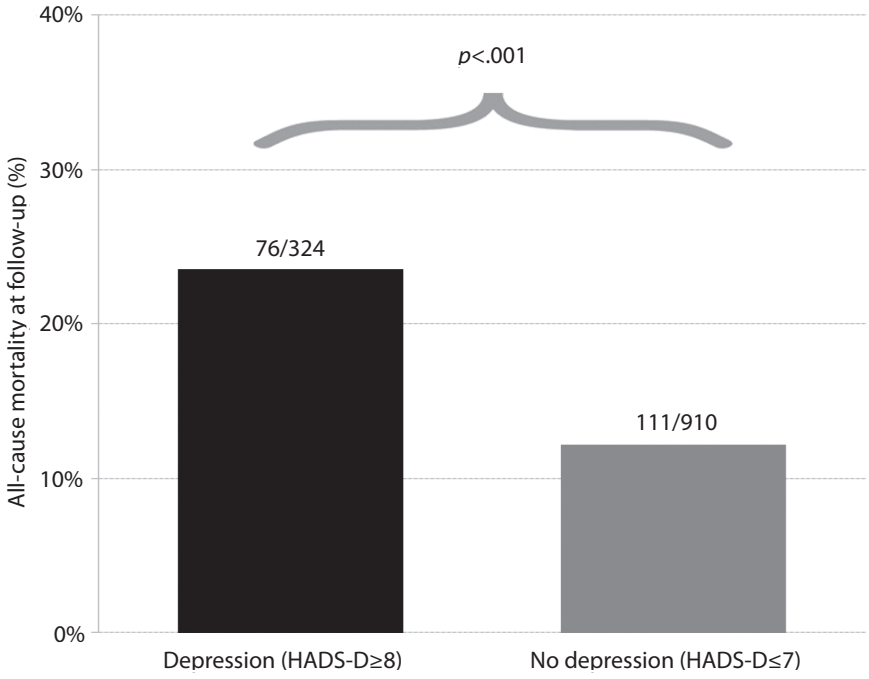
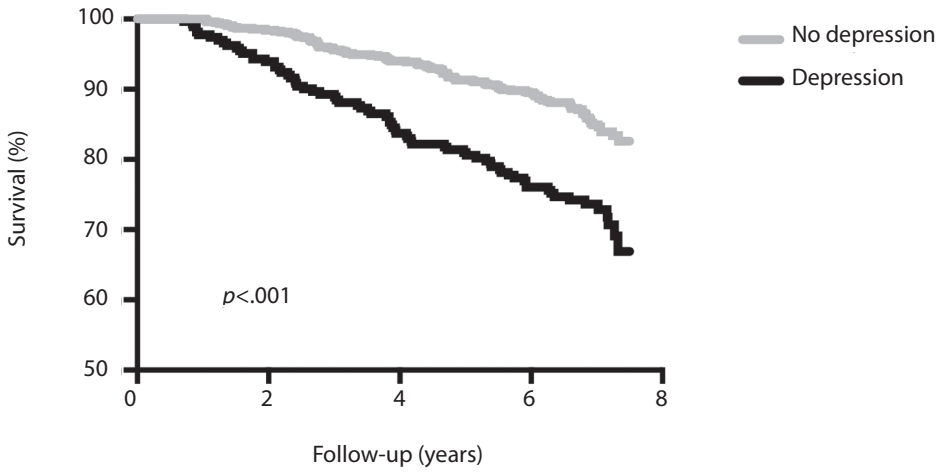


Figure 3. Cumulative survival curve for all-cause mortality and stratified by depression



Patients at risk (n)

Depression	301	269	233
No depression	885	846	733

Table 2. Associates of all-cause mortality (adjusted analysis)

	HR	95%CI	*p*
Socio-demographic characteristics			
Male gender	2.21	1.30 – 3.78	.004**
Age	1.08	1.05 – 1.10	<.001***
Clinical characteristics			
Sirolimus-eluting stent	.76	.48 - 1.19	.23
Multi-vessel disease	1.25	.79 – 1.96	.34
Cardiac history [a]	1.25	.79 – 1.99	.34
Indication for PCI			
Unstable angina	.84	.54 – 1.31	.44
MI	1.18	.57 – 2.45	.65
Renal failure	.94	.39 – 2.27	.89
Hypertension	1.15	.74 – 1.79	.53
Hypercholesterolemia	1.95	1.05 – 3.61	.034*
Diabetes mellitus	1.85	1.14 – 2.99	.013*
Family history of CAD	.70	.40 – 1.23	.21
Self-reported smoking	1.33	.80 – 2.23	.27
BMI	1.01	.97 – 1.05	.60
Cardiac medication			
ACE-inhibitors	1.40	.89 – 2.19	.15
Beta-blockers	.83	.52 – 1.32	.43
Calcium-antagonists	1.18	.77 – 1.82	.45
Diuretics	1.54	.94 – 2.53	.086
Oral nitrates	.89	.51 – 1.54	.67
Statins	.40	.23 - .69	.001***
Psychological characteristics			
Depression (i.e., HADS-D ≥8)	1.63	1.05 – 2.71	.038*
Anxiety (i.e., HADS-A ≥8)	.92	.52 – 1.62	.77
Type D personality	1.19	.76 – 1.85	.45

*$p \leq .05$; ** $p \leq .01$; ***$p \leq .001$; [a] Previous myocardial infarction (MI), percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG) surgery; ACE = angiotensin-converting enzyme, BMI = body mass index (kg/m^2), CAD = coronary artery disease, HADS-A = Hospital Anxiety and Depression Scale - Anxiety, HADS-D = Hospital Anxiety and Depression Scale - Depression

DISCUSSION

To our knowledge, this is the first study to report on the relationship between depression and long-term mortality in patients treated with PCI and to examine whether this relationship is independent of anxiety and Type D personality. After a median follow-up of 7 years, depression was independently associated with a 1.6-fold increased risk for all-cause mortality in patients who survived the first 6 months post-PCI, after adjusting for relevant socio-demographic and clinical characteristics, anxiety, and Type D personality. Further, male gender, older age, hypercholesterolemia, and diabetes mellitus were significantly associated with an increased risk for all-cause mortality, whereas the prescription of statins was associated with a reduced risk for all-cause mortality. No significant effects were found for anxiety and Type D personality in relation to the endpoint.

The results of the current study corroborate those of previous studies in cardiac patients, demonstrating that depression is independently associated with an increased risk for short-term mortality [1, 2, 6-9, 12, 13]. The impact of depression on long-term mortality (≥5 years) has been studied previously, with these studies mainly focusing on post-MI patients [4, 21], CABG patients [5, 14], and patients referred for exercise testing [22], rather than PCI patients. The results of 3 of these previous studies were in line with the current study, showing a significant association between depression and long-term mortality [5, 14, 21], whereas other studies demonstrated that depression was significantly associated with short-term prognosis but not with long-term prognosis [4, 22]. These discrepancies may be explained by differences in the patient population (284 post-MI patients and 5057 patients referred for exercise testing, respectively) and the assessment of depression using other instruments than the HADS (e.g., Beck Depression Inventory (BDI)).

In the context of CAD, there has been a tendency to focus on one risk factor at a time, which has also been labeled as the 'risk factor of the month approach' [23, 24]. Hence, the question remains whether depression exerts an independent effect on prognosis or whether other psychological risk factors, like anxiety and Type D personality, may explain some of the variance in the association between depression and mortality. With the current study, we were able to demonstrate that depression may exert an independent effect on outcomes, as depression remained independently associated with 7-year all-cause mortality, even when adjusting for related constructs, such as anxiety and Type D personality. Previous studies on the impact of anxiety and Type D personality on prognosis in CAD have shown mixed results [3, 10, 25, 43, 44], with these studies mainly focusing on short-term prognosis. In order to draw firm conclusions, future research should seek to further disentangle the different psychological constructs that have been related to cardiac outcomes and refrain from succumbing to the 'risk factor of the month approach' [24].

Examining the impact of not only multiple psychological risk factors but also their co-occurrence seems worthwhile, as risk factors tend to cluster together and may dispose patients to a higher risk [24, 45].

There are several potential pathways through which depression may have an adverse influence on prognosis in patients with CAD. First, depressed patients may be less likely to engage in optimal health-related behaviors, such as exercising, quitting smoking, and adhering to dietary constrictions and the prescribed medication regimen [9, 14, 46]. However, the current study did not support this notion, as there were no differences in smoking status and BMI between depressed and non-depressed patients. Unfortunately, no other health-related behaviors were assessed in the current study. Second, depression may alter the activity of the sympathetic nervous system in turn leading to increases in heart rate and blood pressure [46]. The hypothalamus-pituitary-adrenal axis may also be involved, as depression may induce hypercortisolemia [47, 48]. Finally, an increase in inflammatory markers, such as interleukin (IL)-6 and C-reactive protein (CRP), in depressed patients may provide another explanation for the adverse effect of depression on CAD prognosis [14, 49]. These potential pathways largely remain speculative as few studies have examined these pathways as potential links between depression and prognosis in CAD.

However, knowledge of the pathways that may explain the association between depression and mortality is essential for secondary prevention. So far, results of psychological intervention trials have shown mixed results. Some trials demonstrated that cognitive-behavioral therapy and antidepressants could (modestly) reduce symptoms of depression in CAD patients, but this did not translate into enhanced survival [50, 51], whereas 2 recent trials showed that treatment of depression was associated with a reduction in cardiovascular morbidity and mortality [52, 53]. Future research into the depression construct is needed to identify optimal targets for intervention. For instance, there is increasing evidence that specific symptoms of depression are more cardiotoxic than others [9, 54, 55]. Also, previous studies suggest that incident depression is predictive of impaired cardiovascular prognosis rather than recurrent depressive episodes [56, 57].

The limitations of the current study must be acknowledged. First, no information on left ventricular ejection fraction (LVEF) was collected, which is an important risk factor for poor prognosis in CAD [10]. However, in multivariable analysis we adjusted for multi-vessel disease and cardiac history as indicators of disease severity. Second, no information on participation in cardiac rehabilitation and prescription of psychotropic medication was collected. Hence, we could not adjust for these potential confounders in multivariable analyses. Third, except for information on smoking and BMI, which might potentially impinge on the relationship between depression and prognosis, we had no information on health-related behaviors, such as adherence to medication. Fourth, information on renal failure was only collected for 783 patients. Finally, 26.3% (441/1675) of the eligible

PCI patients were not included in the study due to death within 6 months (n=54) or non-response to the HADS questionnaire (n=387).

Strengths of the study comprise the prospective study design with a median follow-up duration of 7 years, the large sample size, and the focus on PCI patients. Previous studies on the role of psychological factors in CAD have mainly been conducted in post-MI patients. Moreover, given the paucity of studies on the relationship between depression and long-term prognosis, the findings of the current study add to our understanding of the impact of depression on long-term cardiovascular health outcomes.

In conclusion, the current study showed that after a median follow-up of 7 years, depression was independently associated with a 1.6-fold increased risk for all-cause mortality in patients who survived the first 6 months post-PCI, after adjusting for socio-demographic and clinical characteristics, anxiety, and Type D personality. No effect was found for anxiety and Type D personality on all-cause mortality. Future studies are warranted to further elucidate the impact of depression on long-term mortality and to examine the potential pathways explaining this link.

FUNDING

This research was in part supported with a VIDI grant (91710393) to Prof. Susanne S. Pedersen from the Netherlands Organization for Health Research and Development (ZonMW), The Hague, the Netherlands.

ACKNOWLEDGEMENTS

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [58].

REFERENCES

1. Lespérance F, Frasure-Smith N, Talajic M, Bourassa MG. Five-year risk of cardiac mortality in relation to initial severity and one-year changes in depression symptoms after myocardial infarction. Circulation. 2002;105(9):1049-53.
2. Burg MM, Benedetto MC, Soufer R. Depressive symptoms and mortality two years after coronary artery bypass graft surgery (CABG) in men. Psychosom Med. 2003;65(4):508-10.
3. Jiang W, Kuchibhatla M, Cuffe MS, Christopher EJ, Alexander JD, Clary GL, et al. Prognostic value of anxiety and depression in patients with chronic heart failure. Circulation. 2004;110(22):3452-6.
4. Parakh K, Thombs BD, Fauerbach JA, Bush DE, Ziegelstein RC. Effect of depression on late (8 years) mortality after myocardial infarction. Am J Cardiol. 2008;101(5):602-6.
5. Connerney I, Sloan RP, Shapiro PA, Bagiella E, Seckman C. Depression is associated with increased mortality 10 years after coronary artery bypass surgery. Psychosom Med. 2010;72(9):874-81.
6. Frasure-Smith N, Lespérance F, Gravel G, Masson A, Juneau M, Talajic M, et al. Social support, depression, and mortality during the first year after myocardial infarction. Circulation. 2000;101(16):1919-24.
7. Jiang W, Kuchibhatla M, Clary GL, Cuffe MS, Christopher EJ, Alexander JD, et al. Relationship between depressive symptoms and long-term mortality in patients with heart failure. Am Heart J. 2007;154(1):102-8.
8. Denollet J, Martens EJ, Smith ORF, Burg MM. Efficient assessment of depressive symptoms and their prognostic value in myocardial infarction patients. J Affect Disord. 2010;120(1-3):105-11.
9. Pedersen SS, Denollet J, Daemen J, van de Sande M, de Jaegere PT, Serruys PW, et al. Fatigue, depressive symptoms, and hopelessness as predictors of adverse clinical events following percutaneous coronary intervention with paclitaxel-eluting stents. J Psychosom Res. 2007;62(4):455-61.
10. Strik JJMH, Denollet J, Lousberg R, Honig A. Comparing symptoms of depression and anxiety as predictors of cardiac events and increased health care consumption after myocardial infarction. J Am Coll Cardiol. 2003;42(10):1801-7.
11. Frasure-Smith N, Lespérance F, Talajic M. Depression and 18-month prognosis after myocardial infarction. Circulation. 1995;91(4):999-1005.
12. Carney RM, Blumenthal JA, Freedland KE, Youngblood M, Veith RC, Burg MM, et al. Depression and late mortality after myocardial infarction in the Enhancing Recovery in Coronary Heart Disease (ENRICHD) Study. Psychosom Med. 2004;66(4):466-74.
13. Grace SL, Abbey SE, Kapral MK, Fang J, Nolan RP, Stewart DE. Effect of depression on five-year mortality after an acute coronary syndrome. Am J Cardiol. 2005;96(9):1179-85.
14. Blumenthal JA, Lett HS, Babyak MA, White W, Smith PK, Mark DB, et al. Depression as a risk factor for mortality after coronary artery bypass surgery. Lancet. 2003;362(9384):604-9.
15. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: A meta-analysis. Psychosom Med. 2004;66(6):802-13.
16. van Melle JP, de Jonge P, Spijkerman TA, Tijssen JGP, Ormel J, van Veldhuisen DJ, et al. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: A meta-analysis. Psychosom Med. 2004;66(6):814-22.
17. Meijer A, Conradi HJ, Bos EH, Thombs BD, van Melle JP, de Jonge P. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: A meta-analysis of 25 years of research. Gen Hosp Psychiatry. 2011;33(3):203-16.
18. Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: A meta-analysis of 6362 events among 146.538 participants in 54 observational studies. Eur Heart J. 2006;27(23):2763-74.
19. Damen NL, Pelle AJ, van Geuns R-JM, van Domburg RT, Boersma E, Pedersen SS. Intra-individual changes in anxiety and depression during 12-month follow-up in percutaneous coronary intervention patients. J Affect Disord. 2011;134(1-3):464-7.
20. Kaptein KI, de Jonge P, van den Brink RHS, Korf J. Course of depressive symptoms after myocardial infarction and cardiac prognosis: A latent class analysis. Psychosom Med. 2006;68(5):662-8.

21. Barefoot JC, Helms MJ, Mark DB, Blumenthal JA, Califf RM, Haney TL, et al. Depression and long-term mortality risk in patients with coronary artery disease. Am J Cardiol. 1996;78(6):613-7.
22. Herrmann C, Brand-Driehorst S, Buss U, Rüger U. Effects of anxiety and depression on 5-year mortality in 5057 patients referred for exercise testing. J Psychosom Res. 2000;48(4-5):455-62.
23. Denollet J, Brutsaert DL. Personality, disease severity, and the risk of long-term cardiac events in patients with a decreased ejection fraction after myocardial infarction. Circulation. 1998;97(2):167-73.
24. Rozanski A, Blumenthal JA, Davidson KW, Saab PG, Kubzansky L. The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: The emerging field of behavioral cardiology. J Am Coll Cardiol. 2005;45(5):637-51.
25. Denollet J, Pedersen SS, Vrints CJ, Conraads VM. Usefulness of Type D personality in predicting five-year cardiac events above and beyond concurrent symptoms of stress in patients with coronary heart disease. Am J Cardiol. 2006;97(7):970-3.
26. Ong ATL, van Domburg RT, Aoki J, Sonnenschein K, Lemos PA, Serruys PW. Sirolimus-eluting stents remain superior to bare-metal stents at two years: Medium-term results from the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry. J Am Coll Cardiol. 2006;47(7):1356-60.
27. Lemos PA, Serruys PW, van Domburg RT, Saia F, Arampatzis CA, Hoye A, et al. Unrestricted utilization of sirolimus-eluting stents compared with conventional bare stent implantation in the "real world": The Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry. Circulation. 2004;109(2):190-5.
28. Rumsfeld JS, Magid DJ, Plomondon ME, Sacks J, Henderson W, Hlatky MA, et al. Health-related quality of life after percutaneous coronary intervention versus coronary bypass surgery in high-risk patients with medically refractory ischemia. J Am Coll Cardiol. 2003;41(10):1732-8.
29. Goodyear MDE, Krleza-Jeric K, Lemmens T. The declaration of Helsinki. Br Med J. 2007;335(7621):624-5.
30. Nelson RG, Tuttle KR. The new KDOQI clinical practice guidelines and clinical practice recommendations for diabetes and CKD. Blood Purif. 2007;25(1):112-4.
31. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-70.
32. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med. 1997;27(2):363-70.
33. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res. 2002;52(2):69-77.
34. Herrmann C. International experiences with the Hospital Anxiety and Depression Scale - A review of validation data and clinical results. J Psychosom Res. 1997;42(1):17-41.
35. Emons WHM, Meijer RR, Denollet J. Negative affectivity and social inhibition in cardiovascular disease: Evaluating Type-D personality and its assessment using item response theory. J Psychosom Res. 2007;63(1):27-39.
36. Denollet J, Pedersen SS, Ong AT, Erdman RA, Serruys PW, van Domburg RT. Social inhibition modulates the effect of negative emotions on cardiac prognosis following percutaneous coronary intervention in the drug-eluting stent era. Eur Heart J. 2006;27(2):171-7.
37. Denollet J. DS14: Standard assessment of negative affectivity, social inhibition, and Type D personality. Psychosom Med. 2005;67(1):89-97.
38. de Jonge P, Denollet J, van Melle JP, Kuyper A, Honig A, Schene AH, et al. Associations of Type D personality and depression with somatic health in myocardial infarction patients. J Psychosom Res. 2007;63(5):477-82.
39. Martens EJ, Kupper N, Pedersen SS, Aquarius A, Denollet J. Type-D personality is a stable taxonomy in post-MI patients over an 18-month period. J Psychosom Res. 2007;63(5):545-50.

40. Babyak MA. What you see may not be what you get: A brief, nontechnical introduction to overfitting in regression-type models. Psychosom Med. 2004;66(3):411-21.
41. Freedland KE, Babyak MA, McMahon RJ, Jennings JR, Golden RN, Sheps DS. Statistical guidelines for psychosomatic medicine. Psychosom Med. 2005;67(2):167.
42. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol. 1996;49(12):1373-9.
43. Coyne JC, Jaarsma T, Luttik M, van Sonderen E, van Veldhuisen DJ, Sanderman R. Lack of prognostic value of Type D personality for mortality in a large sample of heart failure patients. Psychosom Med. 2011;73(7):557-62.
44. Grande G, Romppel M, Vesper J, Schubmann R, Glaesmer H, Herrmann-Lingen C. Type D personality and all-cause mortality in cardiac patients - Data from a German cohort study. Psychosom Med. 2011;73(7):548-56.
45. Pedersen SS, Denollet J, van Gestel YR, Serruys PW, van Domburg RT. Clustering of psychosocial risk factors enhances the risk of depressive symptoms 12-months post percutaneous coronary intervention. Eur J Cardiovasc Prev Rehabil. 2008;15(2):203-9.
46. Carney RM, Freedland KE, Miller GE, Jaffe AS. Depression as a risk factor for cardiac mortality and morbidity: A review of potential mechanisms. J Psychosom Res. 2002;53(4):897-902.
47. Jokinen J, Nordström P. HPA axis hyperactivity and cardiovascular mortality in mood disorder inpatients. J Affect Disord. 2009;116(1 2):88-92.
48. Brown ES, Varghese FP, McEwen BS. Association of depression with medical illness: Does cortisol play a role? Biol Psychiatry. 2004;55(1):1-9.
49. Appels A, Bär FW, Bär J, Bruggeman C, de Baets M. Inflammation, depressive symptomatology, and coronary artery disease. Psychosom Med. 2000;62(5):601-5.
50. ENRICHD Investigators. Effects of treating depression and low perceived social support on clinical events after myocardial infarction. J Am Med Assoc. 2003;289(23):3106-16.
51. Rollman BL, Belnap BH, LeMenager MS, Mazumdar S, Houck PR, Counihan PJ, et al. Telephone-delivered collaborative care for treating post-CABG depression. J Am Med Assoc. 2009;302(19):2095-103.
52. Davidson KW, Rieckmann N, Clemow L, Schwartz JE, Shimbo D, Medina V, et al. Enhanced depression care for patients with acute coronary syndrome and persistent depressive symptoms: Coronary psychosocial evaluation studies randomized controlled trial. Arch Intern Med. 2010;170(7):600-8.
53. Gullikson M, Burell G, Vessby B, Lundin L, Toss H, Svardsudd K. Randomized controlled trial of cognitive behavioral therapy vs standard treatment to prevent recurrent cardiovascular events in patients with coronary heart disease: Secondary Prevention in Uppsala Primary Health Care Project (SUPRIM). Arch Intern Med. 2011;171(2):134-40.
54. Doyle F, Conroy R, McGee H, Delaney M. Depressive symptoms in persons with acute coronary syndrome: Specific symptom scales and prognosis. J Psychosom Res. 2010;68(2):121-30.
55. Roest AM, Thombs BD, Grace SL, Stewart DE, Abbey SE, de Jonge P. Somatic/affective symptoms, but not cognitive/affective symptoms, of depression after acute coronary syndrome are associated with 12-month all-cause mortality. J Affect Disord. 2011;131(1-3):158-63.
56. de Jonge P, van den Brink RHS, Spijkerman TA, Ormel J. Only incident depressive episodes after myocardial infarction are associated with new cardiovascular events. J Am Coll Cardiol. 2006;48(11):2204-8.
57. Carney RM, Freedland KE, Steinmeyer B, Blumenthal JA, de Jonge P, Davidson KW, et al. History of depression and survival after acute myocardial infarction. Psychosom Med. 2009;71(3):253-9.
58. Shewan LG, Coats AJS. Ethics in the authorship and publishing of scientific articles. Int J Cardiol. 2010;144(1):1-2.

CHAPTER 4

Depression and 7-year mortality for patients treated with percutaneous coronary intervention

Kawada T. Int J Cardiol. 2012;167(6):3041.
Letter to the Editor

To the Editor,

I read the recently published article by Damen et al. [1] about depression as a significant predictor of 7-year all-cause mortality in patients with percutaneous coronary intervention. They used the Hospital Anxiety and Depression Scale (HADS) to assess anxiety and depression and the Type D scale (DS14) to assess Type D personality. As a conclusion, depression was significantly associated with a 1.6-fold increased risk of mortality by multivariable Cox regression analysis. Other risk factors were male, age, hypercholesterolemia, diabetes mellitus, and statin medication.

The number of events was satisfactory for the analysis, and tools for identifying psychological characteristics were appropriate with valid evidence. The authors concluded that further elucidation is needed to understand the potential pathways linking depression to long-term mortality following PCI.

I have two queries on their article. First, Grande et al. recently conducted a meta-analysis using 12 prospective studies on prognostic ability of Type D personality in patients with cardiovascular disease [2]. Although odds ratio of Type D scale for the prognosis decreased overtime, significant association between Type D personality and prognosis was observed. Six studies out of 12 used depression scale score as a psychological variable to adjust the statistical model. The discrepancy should be explored as a further study.

Second, Romppel et al. reported a 6-year longitudinal study to know the association between Type D personality and depressive symptoms for cardiac patients [3]. Depressive symptoms were assessed by a subscale of HADS (HADS-D), and they used HADS-D both at baseline and follow-up studies. Although Type D personality measured by DS14 was significantly associated with HADS-D at follow-up study, the relationship between DS14 and HADS-D at baseline was weak. This means that there is a possibility of change in the state of depression in patients with percutaneous coronary intervention at baseline, which was conducted by Damen et al. [1]. Not only for baseline study, but also another opportunity to conduct depression survey is needed to know the persistency of depression during follow-up period. As the effect of depression on mortality for cardiac patient is important from the view point of preventive cardiology, further study is needed to clarify the association.

The author of this manuscript has certified that he comply with the principles of ethical publishing in the International Journal of Cardiology.

REFERENCES

1. Damen NL, Versteeg H, Boersma E, Serruys PW, van Geuns RJ, Denollet J, et al. Depression is independently associated with 7-year mortality in patients treated with percutaneous coronary intervention: Results from the RESEARCH registry. Int J Cardiol. 2012;167(6):2496-501.
2. Grande G, Romppel M, Barth J. Association between Type D personality and prognosis in patients with cardiovascular diseases: A systematic review and meta-analysis. Ann Behav Med. 2012;43(3):299-310.
3. Romppel M, Herrmann-Lingen C, Vesper J, Grande G. Type D personality and persistence of depressive symptoms in a German cohort of cardiac patients. J Affect Disord. 2012;136(3):1183-7.

CHAPTER 4

In reply to the Letter to the Editor of Dr. Kawada: "Depression and 7-year mortality for patients treated with percutaneous coronary intervention"

Damen NL, Pedersen SS. Int J Cardiol. 2013;168(3):2880-1.
Reply to the Letter to the Editor

In our recent study on the relationship between depression and 7-year mortality in patients treated with percutaneous coronary intervention (PCI), we adjusted for the distressed (Type D) personality in multivariable analyses. As Dr. Kawada correctly stated in his letter to the editor [1], we did not find a significant association between Type D personality and all-cause mortality, which is in contrast to some [2-5] but not all previous studies [6-8]. In the meta-analysis by Grande et al., the authors concluded that although there is a significant association between Type D personality and prognosis in cardiac patients, the strength of this effect has been declining over the years and that therefore, the effect of Type D might have been overestimated in previous studies [9].

In our view, it is possible that Type D personality might affect prognosis in specific cardiac populations, but that this effect might not generalize to all groups. As discussed in the meta-analysis by Grande et al., an effect for Type D personality on prognosis was mainly found in patients with acute coronary syndrome (ACS), such as post myocardial infarction (MI) and coronary artery bypass graft (CABG) surgery patients, but not in heart failure (HF) patients [9]. Given these findings, Type D personality may mainly exert an effect on patients in the early stages of disease, whereas no or smaller effects are found in end-stage heart disease, such as HF.

With our study, we were not able to confirm the findings of an earlier study of the RESEARCH registry, in which a significant association was found between Type D personality and the composite endpoint of cardiac mortality and MI [10]. An association between cardiac-related endpoints and Type D personality was also confirmed in other previous studies [2, 4, 5]. However, in the present study the endpoint was all-cause mortality at 7-year follow-up. It is plausible that Type D personality is more related to cardiac causes of death rather than to all-cause mortality [7]. Future studies are needed to contribute to a better understanding of the role of personality characteristics in the context of CAD.

We further agree with Dr. Kawada that it is important to look at the persistence of depressive symptoms and their effect on prognosis in CAD rather than only at baseline or a one-time snapshot. We have previously demonstrated that levels of depression remain stable over time for the majority of PCI patients (around 80%) [11], which was also found in other cardiac patient groups, including ICD [12, 13], post-MI [14], and CABG patients [15]. Our study was underpowered to look at the prognostic value of persistent depressive symptoms, so future studies on this topic are warranted.

REFERENCES

1. Kawada T. Depression and 7-year mortality for patients treated with percutaneous coronary intervention. Int J Cardiol. 2012;167(6):3041.
2. Denollet J, Pedersen SS, Vrints CJ, Conraads VM. Usefulness of Type D personality in predicting five-year cardiac events above and beyond concurrent symptoms of stress in patients with coronary heart disease. Am J Cardiol. 2006;97(7):970-3.
3. Denollet J, Schiffer AA, Spek V. A general propensity to psychological distress affects cardiovascular outcomes. Circ Cardiovasc Qual Outcomes. 2010;3(5):546-57.
4. Martens EJ, Mols F, Burg MM, Denollet J. Type D personality predicts clinical events after myocardial infarction, above and beyond disease severity and depression. J Clin Psychiatry. 2010;71(6):778-83.
5. Denollet J, Vaes J, Brutsaert DL. Inadequate response to treatment in coronary heart disease - Adverse effects of type D personality and younger age on 5-year prognosis and quality of life. Circulation. 2000;102(6):630-5.
6. Coyne JC, Jaarsma T, Luttik M, van Sonderen E, van Veldhuisen DJ, Sanderman R. Lack of prognostic value of Type D personality for mortality in a large sample of heart failure patients. Psychosom Med. 2011;73(7):557-62.
7. Grande G, Romppel M, Vesper J, Schubmann R, Glaesmer H, Herrmann-Lingen C. Type D personality and all-cause mortality in cardiac patients—Data from a German cohort study. Psychosom Med. 2011;73(7):548-56.
8. Pelle AJ, Pedersen SS, Schiffer AA, Szabo B, Widdershoven JW, Denollet J. Psychological distress and mortality in systolic heart failure. Circ Heart Fail. 2010;3(2):261-7.
9. Grande G, Romppel M, Barth J. Association between Type D personality and prognosis in patients with cardiovascular diseases: A systematic review and meta-analysis. Ann Behav Med. 2012;43(3):299-310.
10. Pedersen SS, Lemos PA, van Vooren PR, Liu TKK, Daemen J, Erdman RAM, et al. Type D personality predicts death or myocardial infarction after bare metal stent or sirolimus-eluting stent implantation: A rapamycin-eluting stent evaluated at rotterdam cardiology hospital (RESEARCH) registry substudy. J Am Coll Cardiol. 2004;44(5):997-1001.
11. Damen NL, Pelle AJ, van Geuns RM, van Domburg RT, Boersma E, Pedersen SS. Intra-individual changes in anxiety and depression during 12-month follow-up in percutaneous coronary intervention patients. J Affect Disord. 2011;134(1–3):464-7.
12. Pedersen SS, van den Broek KC, Theuns DA, Erdman RA, Alings M, Meijer A, et al. Risk of chronic anxiety in implantable defibrillator patients: A multi-center study. Int J Cardiol. 2009;147(3):420-3.
13. Pedersen SS, Theuns DAMJ, Jordaens L, Kupper N. Course of anxiety and device-related concerns in implantable cardioverter defibrillator patients the first year post implantation. Europace. 2010;12(8):1119-26.
14. Kaptein KI, de Jonge P, van den Brink RHS, Korf J. Course of depressive symptoms after myocardial infarction and cardiac prognosis: A latent class analysis. Psychosom Med. 2006;68(5):662-8.
15. Blumenthal JA, Lett HS, Babyak MA, White W, Smith PK, Mark DB, et al. Depression as a risk factor for mortality after coronary artery bypass surgery. Lancet. 2003;362(9384):604-9.

CHAPTER 5

Reduced positive affect (anhedonia) is independently associated with 7-year mortality in patients treated with percutaneous coronary intervention: Results from the RESEARCH registry

Damen NL, Pelle AJ, Boersma E, Serruys PW, van Domburg RT, Pedersen SS. Eur J Prev Cardiol 2013;20(1):127-34.

ABSTRACT

Aims: Negative mood states (e.g., anxiety and depression) have been associated with increased cardiovascular morbidity and mortality in coronary artery disease (CAD), but little is known about the impact of positive emotions on these health outcomes. We examined whether anhedonia (i.e., reduced positive affect) was associated with 7-year mortality in patients treated with percutaneous coronary intervention (PCI).

Methods: Consecutive PCI patients (N=1206; 71.5% men; mean age 62.0±11.1 years) from the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry completed the Hospital Anxiety and Depression Scale (HADS) to assess anhedonia at baseline. Anhedonia was defined as a score ≤7 (i.e., 1 SD below the mean) on the positive affect scale of the HADS. The endpoint was defined as all-cause mortality.

Results: The prevalence of anhedonia was 23.7% (286/1206). After a median follow-up of 7.0±1.6 years, 186 deaths (15.4%) from any cause were recorded. The incidence of mortality in anhedonic patients was 22.7% (65/286) versus 13.2% (121/920) in non-anhedonic patients (HR=1.66; 95%CI [1.19-2.32], p=.003). Cumulative hazard functions were significantly different for anhedonic versus non-anhedonic patients (log-rank X^2=16.61, p<.001). In multivariable analysis, anhedonia remained independently associated with all-cause mortality (HR=1.51; 95%CI[1.03-2.22], p=.036), after adjusting for socio-demographic and clinical characteristics, and negative and relaxed affect.

Conclusion: Anhedonia was independently associated with a 1.5-fold increased risk for all-cause mortality in patients who survived the first 6 months post-PCI. Enhancing positive emotions, in addition to reducing negative emotions, may constitute an important target for future psychological intervention trials in CAD patients.

INTRODUCTION

Negative mood states, like anxiety and depression, have been associated with increased cardiovascular morbidity and mortality in coronary artery disease (CAD) [1-3]. Only a paucity of studies focused on the impact of positive emotions on these outcomes [4, 5]. Positive affect refers to mood states such as joy, activity, and cheerfulness [6], and is not merely the opposite of negative affect [7], as both types of affect can be present simultaneously [8].

High levels of positive affect have been associated with a decrease in hospital readmissions in patients with CAD [9], lower incident hypertension [10], a dampened physiological stress response [11], and lower incident CAD [12], whereas studies on the association between positive affect and survival showed mixed results [5, 13]. Anhedonia (i.e., reduced positive affect) has been shown to independently predict all-cause mortality and major adverse clinical events (i.e., myocardial infarction, hospitalization, or coronary revascularization) 1 year after an acute cardiac event [14]. In patients treated with percutaneous coronary intervention (PCI), anhedonia was associated with an increased risk for the composite of death and myocardial infarction (MI) 2 years post-index event [4]. In addition, anhedonia has been associated with poor patient-reported outcomes, such as poor health status [15, 16].

It is not yet known whether anhedonia is associated with long-term mortality in addition to short-term mortality in CAD patients. Therefore, the aim of the current study was to examine whether anhedonia is associated with 7-year mortality in patients treated with PCI with drug-eluting stenting.

METHODS

Participants and procedure

The study sample comprised consecutive patients treated with PCI, with either sirolimus-eluting stenting (SES) or bare-metal stenting (BMS), between September 2, 2001 and November 14, 2002 at the Erasmus MC, Rotterdam, the Netherlands, as part of the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry. The design of the RESEARCH registry has been published previously [17, 18]. In brief, the registry was designed to evaluate the efficacy and safety of SES implantation in the "real world" of interventional cardiology. Hence, no exclusion criteria were applied for patients entering the registry, and all PCI patients were eligible for enrolment regardless of anatomical or clinical presentation [18, 19].

At 6 months post-PCI (referred to as baseline in the remainder of the paper), all living patients were asked to complete a standardized and validated psychological questionnaire. Due to logistic reasons and in accordance with previous studies on long-

term clinical outcomes in PCI patients, assessment at 6 months was chosen so as to represent patients in a stable condition, as the risk for restenosis is increased in the 0-6 month period post-PCI [20]. All patients were prospectively followed for adverse clinical events. The study protocol was approved by the medical ethics committee of the Erasmus MC, Rotterdam, and the study was conducted according to the Helsinki Declaration [21]. Every patient provided informed consent.

Measures

Socio-demographic and clinical characteristics

Socio-demographic variables included gender and age. Clinical variables included type of stent (BMS vs. SES implantation), multi-vessel disease (multi-vessel disease vs. single-vessel disease/no vessel disease), body mass index (BMI), cardiac history (i.e., previous MI, coronary artery bypass graft (CABG) surgery, or PCI), indication for PCI (stable angina/silent ischemia, unstable angina, or MI), CAD risk factors (i.e., hypertension, hypercholesterolemia, diabetes mellitus, family history of CAD, and self-reported smoking), and prescribed cardiac discharge medications (i.e., aspirin, ACE-inhibitors, beta-blockers, calcium-antagonists, diuretics, oral nitrates, and statins). Information on clinical variables was prospectively collected at the time of the index-PCI and recorded in the institutional database.

Anhedonia

Reduced positive affect, or anhedonia, was assessed using the Hospital Anxiety and Depression Scale (HADS) at baseline. The HADS consists of 14 items that are scored on a 4-point Likert scale ranging from 0 to 3 [22, 23]. Previous research to determine the factor structure of the HADS supported the ability of this questionnaire to assess (the absence of) positive affect in CAD [4, 22, 24-27]. Three of the previous studies were conducted in independent cohorts of patients with CAD (i.e., 355 post-MI patients [24], 875 PCI patients [4], and 534 PCI patients [27], respectively) and indicated that 3 distinct factors can be identified: Positive affect, negative affect, and relaxed affect. The study by Denollet and colleagues in PCI patients was also based on data from the RESEARCH registry, but focused on a subset of patients with a 2-year follow-up. In line with these previous studies, the positive affect scale was computed by summing up 4 items (i.e., items 2, 4, 6, and 12) (range [0-12], mean=9.4±2.8). Anhedonia was defined as a score ≤7 (i.e., 1 SD below the mean) on the positive affect scale. The mean scores on the negative affect scale (range [0-12], mean=3.1±2.8) and the relaxed affect scale (range [0-9], mean=6.5±2.1) were in line with those reported previously [4, 24,27] . The positive affect scale was strongly correlated with the negative affect and the relaxed affect scales (r=-.59 and r=.57, respectively), whereas the negative affect scale showed a large inverse correlation with the relaxed affect scale (r=-.54).

The 3 derived HADS subscales were shown to be internally consistent, with Cronbach's alpha ranging from .72 for the relaxed affect subscale to .86 for the positive affect and the negative affect scales, which was also consistent with previous findings [4, 24, 27].

Endpoint

The endpoint was defined as all-cause mortality. Deaths (n=54) occurring between PCI and psychological assessment were excluded as an endpoint from the analyses. Information on survival status was obtained from the Municipal Civil Registries in May 2009. The median follow-up period for all-cause mortality was 7.0±1.6 years (range [.7-8.0] years). Information on survival status at follow-up was complete (100%) for all patients.

Statistical analyses

Missing values on the HADS

In the current study, the proportion of patients with a missing score on 1 of the 14 items of the HADS questionnaire was in the range from .2-1.8%. For the 4-item scales positive affect and negative affect, missing values were extrapolated with the mean score of completed items when there was a response missing on a maximum of 2 items. For the 3-item scale relaxed affect, missing values were extrapolated with the mean score when there was a response missing on a maximum of 1 item. After extrapolating the missing responses on the 3 HADS subscales, all patients could be included in the analyses.

General analyses

Group differences were examined using the Chi-square test for nominal variables and Student's t-test for independent samples for continuous variables. Cumulative survival curves for anhedonia (i.e., absent versus present) were constructed using the Kaplan-Meier method. The log-rank test was used to compare cumulative survival curves between groups. Univariable and multivariable Cox regression models were used to examine the effect of anhedonia on all-cause mortality. Covariates were entered into the model using the Enter method, thereby reducing the risk of overfitting [28]. In multivariable analysis, we adjusted for socio-demographic characteristics (i.e., gender and age), clinical characteristics (i.e., type of stent, multi-vessel disease, cardiac history, indication for PCI, hypertension, hypercholesterolemia, diabetes mellitus, family history of CAD, self-reported smoking, BMI, and prescribed cardiac medications), and negative and relaxed affect. Covariates were selected a priori based on the literature [4, 14, 29, 30]. Since almost all patients (i.e., 95%) were prescribed aspirin, we did not add aspirin as a covariate to the multivariable model. To be able to compare our results with findings of previous studies, anhedonia was entered as a dichotomous variable in all analyses [4, 14].

Hazard Ratios (HRs) with their corresponding 95% CIs were reported for Cox regression analyses. All results were based on 2-tailed tests and a *p*-value <.05 was used to indicate statistical significance. All statistical analyses were performed using SPSS for Windows 17.0 (SPSS Inc., Chicago, Illinois, USA).

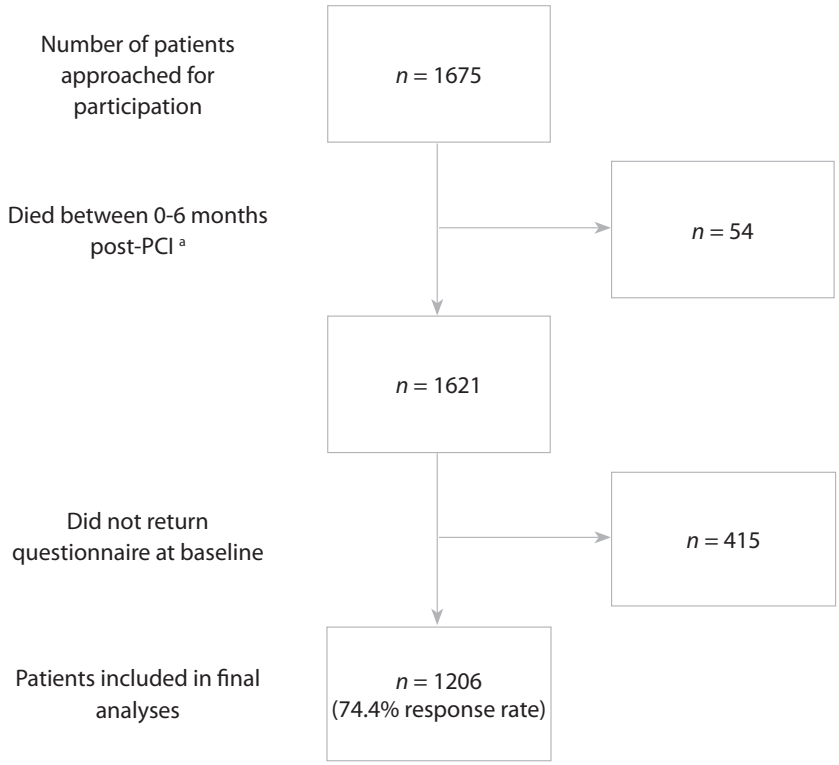
RESULTS

Patient characteristics

Of 1675 eligible patients treated with PCI in the study period, 54 died within 6 months. The remaining 1621 patients were asked to participate in the study, of which 415 patients did not return the questionnaire at baseline (74.4% response rate). Final analyses were based on data from 1206 patients (71.5% men; mean age 62.0±11.1 years, range [26-90] years). In Figure 1, a flowchart of the patient selection is provided. No systematic differences between participants and non-participants were found, except for non-participants more often having diabetes mellitus as compared with participants (21.0% vs. 14.8%, $p<.05$).

In the current sample, the prevalence of anhedonia was 23.7% (286/1206). At follow-up, 186 deaths (15.4%) from any cause were recorded. Patient characteristics stratified by anhedonia are presented in Table 1. Anhedonic and non-anhedonic patients differed on some baseline characteristics, with anhedonic patients more often being female, older, having a cardiac history, and diabetes mellitus, but less often having a family history of CAD and being prescribed statins. Negative affect was more often present in anhedonic patients, whereas relaxed affect was less often present than in non-anhedonic patients (all *p*s<.05).

Figure 1. Flowchart of patient selection



[a] before questionnaire completion at baseline

Table 1. Patient characteristics for the total sample and stratified by anhedonia [a]

	Total sample (N=1206)	***Anhedonia (n=286)***	***No anhedonia (n=920)***	***p***
Socio-demographic characteristics				
Male gender	862 (71.5)	186 (65.0)	676 (73.5)	.007**
Age, mean (SD)	62.0 (11.1)	63.6 (11.3)	61.6 (11.0)	.006**
Clinical characteristics				
Sirolimus-eluting stent	701 (58.1)	180 (62.9)	521 (56.6)	.069
Multi-vessel disease	654 (54.2)	164 (57.3)	490 (53.3)	.25
Cardiac history [b]	680 (57.4)	182 (65.2)	498 (55.0)	.003**
Indication for PCI				.23
Stable angina/ Silent ischemia	609 (50.7)	152 (53.3)	457 (49.9)	
Unstable angina	430 (35.8)	103 (36.1)	327 (35.7)	
MI	162 (13.5)	30 (10.5)	132 (14.4)	
Hypertension	503 (41.7)	132 (46.2)	371 (40.4)	.096
Hypercholesterolemia	974 (80.8)	227 (79.4)	747 (81.3)	.53
Diabetes mellitus	178 (14.8)	57 (19.9)	121 (13.2)	.006**
Family history of CAD	348 (28.9)	66 (23.1)	282 (30.7)	.016*
Self-reported smoking	365 (30.3)	93 (32.5)	272 (29.6)	.39
BMI, mean (SD)	27.1 (5.2)	27.1 (5.2)	27.1 (5.2)	.99
Negative affect	1006 (83.5)	285 (99.7)	721 (78.5)	<.001***
Relaxed affect	985 (81.8)	158 (55.6)	827 (89.9)	<.001***
Cardiac medication				
Aspirin	1135 (94.9)	268 (94.0)	867 (95.2)	.55
ACE-inhibitors	391 (32.7)	84 (29.5)	307 (33.7)	.21
Beta-blockers	796 (66.6)	180 (63.2)	616 (67.6)	.19
Calcium-antagonists	605 (50.6)	144 (50.5)	461 (50.6)	1.00
Diuretics	180 (15.1)	45 (15.8)	135 (14.8)	.76

*$p \leq .05$; ** $p \leq .01$; ***$p \leq .001$

[a] Results are presented as n (%) unless otherwise stated

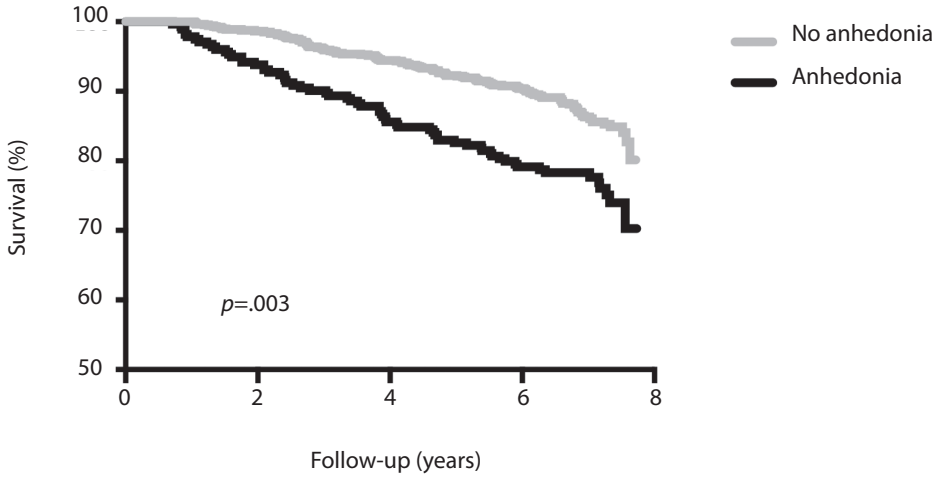
[b] Previous myocardial infarction (MI), percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG) surgery

ACE = angiotensin-converting enzyme, BMI = body mass index (kg/m^2), CAD = coronary artery disease

Anhedonia and all-cause mortality

The incidence of all-cause mortality at follow-up in anhedonic patients was 22.7% (65/286) versus 13.2% (121/920) in non-anhedonic patients. Cumulative hazard functions differed significantly for anhedonic versus non-anhedonic patients (log-rank X^2=16.61, p<.001). In univariable Cox regression analysis, anhedonia was associated with a cumulative increased risk for all-cause mortality (HR=1.66; 95%CI [1.19-2.32], p=.003) (Figure 2). In multivariable Cox regression analysis, anhedonia remained independently associated with all-cause mortality (HR=1.51; 95%CI [1.03-2.22], p=.036), after adjusting for socio-demographic and clinical characteristics, and negative and relaxed affect (Table 2). Male gender, older age, and diabetes mellitus were significantly associated with an increased risk for all-cause mortality as well, whereas the prescription of beta-blockers and statins were associated with a decreased risk for all-cause mortality.

Figure 2. Cumulative survival curve for all-cause mortality and stratified by anhedonia



Patients at risk (n)

Anhedonia	286	262	235	205
No anhedonia	920	893	850	732

Table 2. Associates of all-cause mortality (adjusted analysis)

	HR	95%CI	*p*
Anhedonia	1.51	1.03 – 2.22	.036*
Male gender	2.12	1.40 – 3.20	<.001***
Age	1.07	1.05 – 1.09	<.001***
Sirolimus-eluting stent	.73	.51 - 1.03	.071
Multi-vessel disease	1.31	.92 – 1.86	.14
Cardiac history [a]	1.32	.91 – 1.91	.14
Indication for PCI			
Unstable angina	.83	.59 – 1.18	.30
MI	.93	.51 – 1.67	.80
Hypertension	1.10	.78 – 1.54	.59
Hypercholesterolemia	1.27	.81 – 2.00	.30
Diabetes Mellitus	1.70	1.14 – 2.52	.009**
Family history of CAD	.90	.59 – 1.35	.60
Self-reported smoking	1.07	.72 – 1.60	.74
BMI, mean (SD)	.99	.95 – 1.03	.50
Negative affect	1.13	.72 – 1.77	.59
Relaxed affect	1.23	.78 – 1.95	.38
ACE-inhibitors	1.21	.85 – 1.74	.29
Beta-blockers	.70	.49 - .99	.044*
Calcium-antagonists	1.30	.93 – 1.81	.13
Diuretics	1.25	.83 – 1.90	.29
Oral nitrates	1.03	.68 – 1.57	.88
Statins	.55	.35 - .81	.003**

*$p \leq .05$; ** $p \leq .01$; *** $p \leq .001$

[a] Results are presented as n (%) unless otherwise stated

[b] Previous myocardial infarction (MI), percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG) surgery

ACE = angiotensin-converting enzyme, BMI = body mass index (kg/m^2), CAD = coronary artery disease

DISCUSSION

Studies on the relationship between psychological factors and cardiovascular morbidity and mortality in CAD have primarily focused on the role of negative mood states [1-3]. In contrast, little is known about the impact of positive emotions on CAD prognosis [4, 5]. To our knowledge, this is the first study to report on the relationship between anhedonia (i.e., reduced positive affect) and long-term mortality in patients treated with PCI. After a median follow-up of 7 years, anhedonia was independently associated with a 1.5-fold increased risk for all-cause mortality, after adjusting for socio-demographic and clinical characteristics, and negative and relaxed affect in patients who survived the first 6 months post-PCI.

The results of the current study are in line with previous studies, demonstrating that anhedonia is independently associated with the combined endpoint of major adverse clinical events and all-cause mortality 1 year after an acute cardiac event [14], and the composite of death and MI 2 years post-PCI [4]. Other studies in CAD showed that anhedonia is associated with poor health status [15, 16], whereas a high level of positive affect is associated with a decrease in hospital readmissions [9], lower incident hypertension [10], a dampened physiological stress response [11], and lower incident CAD [12]. However, the current findings also extend previous research by showing that anhedonia is not only associated with short-term but also with long-term prognosis in CAD. In addition, anhedonia exerted an independent effect on prognosis above and beyond negative affect, supporting the notion that positive and negative affect are not merely opposites on the same continuum [7]. Future studies on the combined effects of positive and negative affect are warranted to contribute to a better understanding of the role of different types of affect in the context of CAD [16].

In the current study, we replicated findings on the underlying factorial structure of the HADS. Originally, this instrument was developed to assess symptoms of anxiety and depression [22, 23], but evidence suggests that a subset of the HADS items can also be used as a valid and reliable measure of anhedonia [4, 24, 27]. In line with these previous findings, we identified 3 distinct subscales of the HADS: Positive affect, negative affect, and relaxed affect. Hence, with the HADS it is possible to assess several different psychological constructs without increasing patient burden, making it a useful instrument for clinical practice [16].

There are several potential pathways through which anhedonia may have an adverse influence on CAD prognosis. First, anhedonic patients may be less likely to engage in optimal health-related behaviors, such as exercising, quitting smoking, and adhering to dietary constrictions [4, 6]. However, the current study did not support this notion, as there were no differences in smoking status and BMI between anhedonic and non-anhedonic

patients. Unfortunately, no other health-related behaviors were assessed in the current study. Second, anhedonia may alter the activity of the sympathetic nervous system in turn leading to increases in heart rate and blood pressure [6, 11]. The hypothalamus-pituitary-adrenal axis may also be involved, as anhedonia may induce hypercortisolemia [11]. Finally, an increase in inflammatory markers, such as interleukin (IL)-6 and C-reactive protein (CRP), in anhedonic patients may provide another explanation for the adverse effect of anhedonia on CAD prognosis [31]. These potential pathways remain speculative as they are yet to be tested empirically in future research in this patient population.

Limitations of the current study must be acknowledged. First, no information on left ventricular ejection fraction (LVEF) was collected, which is an important risk factor for poor prognosis in CAD [3]. However, in multivariable analysis we adjusted for multi-vessel disease and cardiac history as indicators of disease severity. Second, no information on participation in cardiac rehabilitation and prescription of psychotropic medication was collected. Hence, we could not adjust for these potential confounders in multivariable analysis. Third, except for information on smoking and BMI, which might potentially impinge on the relationship between anhedonia and prognosis, we had no information on health-related behaviors. Fourth, only information on all-cause mortality was collected and not the specific cause of death. Finally, 28.0% (469/1675) of the eligible PCI patients were not included in the study due to death within 6 months (n=54) or non-response to the HADS questionnaire (n=415).

Strengths of the study comprise the prospective design with a median follow-up duration of 7 years, the large sample size, the focus on PCI patients and positive emotions, in addition to negative emotions. Previous studies on the role of psychological factors in CAD have mainly been conducted in post-MI patients rather than PCI patients, focusing mainly on the role of negative emotions (e.g., anxiety and depression). Given the paucity of studies on the relationship between (reduced) positive emotions and prognosis, the findings of the current study add to the understanding of the impact of different types of emotions on cardiovascular health outcomes.

Future studies are warranted to further examine the impact of anhedonia on adverse health outcomes. If the findings of the current study are confirmed, anhedonia may provide a new target for cardiac rehabilitation and psychological intervention trials. Up to now, trials have mainly focused on the detrimental effects of negative emotions on CAD prognosis, and their efficacy remains unclear [32-34]. The results of the current study confirm and extend the findings of previous studies, indicating that anhedonia is also of importance in the context of CAD both for short- and long-term prognosis. Therefore, psychological interventions should not only target the reduction of negative emotions, but also seek to enhance positive emotions. The first results in this area are promising,

with cognitive-behavioral therapy having been shown to improve positive affect in older depressed patients at increased cardiovascular risk [35], and mindfulness-based stress reduction programs improving positive affect in medically ill patients [36].

Future studies should also seek to further disentangle the different psychological constructs that have been related to cardiac outcomes. Despite overlap between the different psychological constructs, there is not likely to be *one* unifying feature that covers all psychological effects on outcome. Furthermore, psychological constructs are also not necessarily interchangeable and may exert independent effects on outcomes. This independency was also demonstrated in the current study, in which anhedonia remained an independent predictor of all-cause mortality, even when adjusting for the related constructs negative and relaxed affect. To expand our knowledge of the role of psychological factors in CAD, a paucity of recent studies has shifted focus towards the co-occurrence of psychological risk factors rather than single risk factors alone, as risk factors tend to cluster together [37, 38]. For example, in implantable cardioverter defibrillator (ICD) patients the clustering of device-related concerns and Type D personality ("the distressed personality type") was associated with a higher mortality risk as compared to the presence of none or only one of these risk factors [39]. Hence, the impact of clustering of psychological risk factors on cardiac prognosis needs further investigation.

In conclusion, the current study showed that after a median follow-up of 7 years, anhedonia is independently associated with a 1.5-fold increased risk for all-cause mortality, after adjusting for socio-demographic and clinical characteristics, and negative and relaxed affect in patients who survived the first 6 months post-PCI. Future studies are warranted to further determine the impact of anhedonia on adverse health outcomes, and long-term mortality in particular. Enhancing positive emotions, in addition to reducing negative emotions, may constitute an important target for cardiac rehabilitation and future psychological intervention trials in CAD patients.

FUNDING

This research was in part supported with a VIDI grant (91710393) to Prof. Susanne S. Pedersen from the Netherlands Organization for Health Research and Development (ZonMW), The Hague, the Netherlands.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Januzzi JL, Stern TA, Pasternak RC, DeSanctis RW. The influence of anxiety and depression on outcomes of patients with coronary artery disease. Arch Intern Med. 2000;160(13):1913-21.
2. Astin F, Jones K, Thompson DR. Prevalence and patterns of anxiety and depression in patients undergoing elective percutaneous transluminal coronary angioplasty. Heart Lung J Acute Crit Care. 2005;34(6):393-401.
3. Strik JJMH, Denollet J, Lousberg R, Honig A. Comparing symptoms of depression and anxiety as predictors of cardiac events and increased health care consumption after myocardial infarction. J Am Coll Cardiol. 2003;42(10):1801-7.
4. Denollet J, Pedersen SS, Daemen J, de Jaegere P, Serruys PW, van Domburg RT. Reduced positive affect (anhedonia) predicts major clinical events following implantation of coronary-artery stents. J Intern Med. 2008;263(2):203-11.
5. Brummett BH, Boyle SH, Siegler IC, Williams RB, Mark DB, Barefoot JC. Ratings of positive and depressive emotion as predictors of mortality in coronary patients. Int J Cardiol. 2005;100(2):213-6.
6. Pressman SD, Cohen S. Does positive affect influence health? Psychol Bull. 2005;131:925-71.
7. Tellegen A, Watson D, Clark LA. On the dimensional and hierarchical structure of affect. Psychol Sci. 1999;10(4):297-303.
8. Larsen JT, McGraw AP, Cacioppo JT. Can people feel happy and sad at the same time? J Pers Soc Psychol. 2001;81(4):684-96.
9. Middleton R, Byrd K. Psychosocial factors and hospital readmission status of older persons with cardiovascular disease. J Appl Rehabil Counsel. 1996;27:3-10.
10. Smart Richmann L, Kubzansky L, Maselko J, Kawachi I, Choo P, Bauer M. Positive emotion and health: Going beyond the negative. Health Psychol. 2005;24(4):422-9.
11. Rozanski A, Kubzansky LD. Psychologic functioning and physical health: A paradigm of flexibility. Psychosom Med. 2005;67:S47-53.
12. Davidson KW, Mostofsky E, Whang W. Don't worry, be happy: Positive affect and reduced 10-year incident coronary heart disease: The Canadian Nova Scotia Health Survey. Eur Heart J. 2010;31(9):1065-70.
13. Kubzansky LD, Sparrow D, Vokonas P, Kawachi I. Is the glass half empty or half full? A prospective study of optimism and coronary heart disease in the normative aging study. Psychosom Med. 2001;63(6):910-6.
14. Davidson KW, Burg MM, Kronish IM, Shimbo D, Dettenborn L, Mehran R, et al. Association of anhedonia with recurrent major adverse cardiac events and mortality 1 year after acute coronary syndrome. Arch Gen Psychiatry. 2010;67(5):480-8.
15. Versteeg H, Pedersen SS, Erdman RAM, van Nierop J, de Jaegere P, van Domburg RT. Negative and positive affect are independently associated with patient-reported health status following percutaneous coronary intervention. Qual Life Res. 2009;18(8):953-60.
16. Pelle AJ, Pedersen SS, Erdman RAM, Kazemier M, Spiering M, van Domburg RT, et al. Anhedonia is associated with poor health status and more somatic and cognitive symptoms in patients with coronary artery disease. Qual Life Res. 2010;20(5):643-51.
17. Lemos PA, Serruys PW, van Domburg RT, Saia F, Arampatzis CA, Hoye A, et al. Unrestricted utilization of sirolimus-eluting stents compared with conventional bare stent implantation in the "real world": The Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry. Circulation. 2004;109(2):190-5.
18. Ong ATL, van Domburg RT, Aoki J, Sonnenschein K, Lemos PA, Serruys PW. Sirolimus-eluting stents remain superior to bare-metal stents at two years: Medium-term results from the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry. J Am Coll Cardiol. 2006;47(7):1356-60.
19. Pedersen SS, Denollet J, Ong AT, Serruys PW, Erdman RA, van Domburg RT. Impaired health status in Type D patients following PCI in the drug-eluting stent era. Int J Cardiol. 2007;114(3):358-65.

20. Rumsfeld JS, Magid DJ, Plomondon ME, Sacks J, Henderson W, Hlatky MA, et al. Health-related quality of life after percutaneous coronary intervention versus coronary bypass surgery in high-risk patients with medically refractory ischemia. J Am Coll Cardiol. 2003;41(10):1732-8.
21. Goodyear MDE, Krleza-Jeric K, Lemmens T. The declaration of Helsinki. Br Med J. 2007;335(7621):624-5.
22. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-70.
23. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med. 1997;27(2):363-70.
24. Martin CR, Lewin RJP, Thompson DR. A confirmatory factor analysis of the Hospital Anxiety and Depression Scale in coronary care patients following acute myocardial infarction. Psychiatry Res. 2003;120(1):85-94.
25. Dunbar M, Ford G, Hunt K, Der G. A confirmatory factor analysis of the Hospital Anxiety and Depression scale: Comparing empirically and theoretically derived structures. Br J Clin Psychol. 2000;39(1):79-94.
26. Snaith RP, Zigmond AS. The hospital anxiety and depression scale. Br Med J. 1986;292(6516):344.
27. Emons WH, Sijtsma K, Pedersen SS. Dimensionality of the hospital anxiety and depression scale (HADS) in cardiac patients: Comparison of Mokken scale analysis and factor analysis. Assessment. 2012;19(3):337-53.
28. Babyak MA. What you see may not be what you get: A brief, nontechnical introduction to overfitting in regression-type models. Psychosom Med. 2004;66(3):411-21.
29. Freedland KE, Babyak MA, McMahon RJ, Jennings JR, Golden RN, Sheps DS. Statistical guidelines for psychosomatic medicine. Psychosom Med. 2005;67(2):167.
30. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol. 1996;49(12):1373-9.
31. Steptoe A, O'Donnell K, Badrick E, Kumari M, Marmot M. Neuroendocrine and inflammatory factors associated with positive affect in healthy men and women. Am J Epidemiol. 2008;167(1):96-102.
32. ENRICHD Investigators. Effects of treating depression and low perceived social support on clinical events after myocardial infarction. J Am Med Assoc. 2003;289(23):3106-16.
33. Frasure-Smith N, Prince R. The ischemic heart disease life stress monitoring program: Impact on mortality. Psychosom Med. 1985;47(5):431-45.
34. Blumenthal JA, Sherwood A, Babyak MA, Watkins LL, Waugh R, Georgiades A, et al. Effects of exercise and stress management training on markers of cardiovascular risk in patients with ischemic heart disease. J Am Med Assoc. 2005;293(13):1626-34.
35. Strachowski D, Khaylis A, Conrad A, Neri E, Spiegel D, Taylor CB. The effects of cognitive behavior therapy on depression in older patients with cardiovascular risk. Depress Anxiety. 2008;25(8):E1-E10.
36. Grossman P, Tiefenthaler-Gilmer U, Raysz A, Kesper U. Mindfulness training as an intervention for fibromyalgia: Evidence of post-intervention and 3-year follow-up benefits in well-being. Psychother Psychosom. 2007;76(4):226-33.
37. Pedersen SS, Denollet J, van Gestel YR, Serruys PW, van Domburg RT. Clustering of psychosocial risk factors enhances the risk of depressive symptoms 12-months post percutaneous coronary intervention. Eur J Cardiovasc Prev Rehabil. 2008;15(2):203-9.
38. Rozanski A, Blumenthal JA, Davidson KW, Saab PG, Kubzansky L. The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: The emerging field of behavioral cardiology. J Am Coll Cardiol. 2005;45(5):637-51.
39. Pedersen SS, van den Broek KC, Erdman RAM, Jordaens L, Theuns DAMJ. Pre-implantation implantable cardioverter defibrillator concerns and Type D personality increase the risk of mortality in patients with an implantable cardioverter defibrillator. Europace. 2010;12(10):1446-52.

CHAPTER 6

Obesity, health status, and 7-year mortality in percutaneous coronary intervention: In search of an explanation for the obesity paradox

Younge J, Damen NL, van Domburg RT, Pedersen SS. Int J Cardiol 2013;167(4):1154-8.

ABSTRACT

Background: Obesity is a growing health problem and is associated with adverse outcomes in coronary artery disease (CAD). However, recent studies have shown better survival in cardiovascular patients with overweight or obesity, which has been referred to as the "obesity paradox". As there is not a clear understanding of the phenomenon, we examined the association between body mass index (BMI) and all-cause mortality in patients treated with percutaneous coronary intervention (PCI) at 7-years follow-up, and the potential role of health status in explaining the obesity paradox.

Methods: Consecutive PCI patients (72.5% men; mean age 62.0±11.2 years, range [27-90] years) from the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry completed the 36-item Short-Form Health Survey (SF-36) to assess health status at baseline. Patients were classified into a normal weight, overweight, or obesity group.

Results: The prevalence of normal weight was 34.7% (354/1019), whereas overweight was found in 45.9% (468/1019) of patients, and 19.3% (197/1019) was obese. After a median follow-up of 7.0±1.7 years, 163 deaths (16.0%) from any cause were recorded. Cumulative hazard functions differed significantly for the obese and overweight group as compared to the normal weight group (log-rank X^2=6.59, p<.05). In multivariable analysis, overweight but not obesity was associated with a lower risk for all-cause mortality (HR=.60; 95%CI [.42-.86], p=.005). Additionally, after adding the 8 health status SF-36 domains to the multivariate model, the association between overweight and mortality remained unchanged.

Conclusion: In the current study, overweight but not obesity was associated with a lower risk for 7-year mortality in PCI patients. Health status as measured with the SF-36 did not seem to play a role in explaining the obesity paradox.

INTRODUCTION

Obesity is a growing epidemic, with prevalence rates in the general population ranging from 32% in men to 36% in women [1]. In coronary artery disease (CAD), obesity is prevalent in about 30% of patients [2] and is associated with potential risk for cardiovascular morbidity and mortality [3, 4]. However, evidence for a link between obesity and cardiovascular prognosis is based on a small number of studies, with results being mixed, as some [5] but not all studies support such a relationship [6]. Moreover, recent studies have demonstrated that there may not be a linear and straightforward relationship between overweight and obesity and mortality, as some studies show better survival in cardiovascular patients with overweight or obesity. This phenomenon is referred to as the "obesity paradox" [6-9].

In an attempt to explain the obesity paradox, studies have primarily focused on potential differences in the prescription of guideline-based medications [2, 7]. A higher prevalence of invasive treatment has also been observed in obese patients with CAD [2]. Nevertheless, we still do not have a clear understanding of the obesity paradox.

Patient-reported health status might be another avenue to pursue in order to elucidate factors that may impinge on or help explaining the obesity paradox. A recent systematic review demonstrated that poor health status in CAD and congestive heart failure increases the risk of mortality and hospital readmissions, independent of indicators of disease severity and socio-demographic and clinical characteristics [10]. Also a recent paper from our research group found an association between poor health status and higher mortality [11]. A paucity of studies focused on the association between obesity and health status [12-15], but the role of health status in the context of obesity and mortality in CAD has not yet been examined.

Hence, in the current study we examined 1) the association between body mass index (BMI) and all-cause mortality in patients treated with percutaneous coronary intervention (PCI) at 7-year follow-up, and 2) the potential role of health status in explaining the obesity paradox.

METHODS

Study population

The study sample comprised consecutive CAD patients treated with PCI, with either sirolimus-eluting stenting (SES) or bare-metal stenting (BMS), between October 16, 2001 and October 15, 2002 at the Erasmus MC, Rotterdam, the Netherlands, as part of the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry. The design of the RESEARCH registry has been published elsewhere [16]. In brief, the registry was designed to evaluate the efficacy and safety of SES implantation in the "real world" of

interventional cardiology. Hence, no exclusion criteria were applied for patients entering the registry, and all PCI patients were eligible for enrolment regardless of anatomical or clinical presentation [17].

At 6 months post-PCI (referred to as baseline in the remainder of the paper), all living patients were asked to complete a standardized and validated health status measure. In accordance with previous studies, assessment at 6 months was chosen so as to represent patients in a stable condition, as the risk for restenosis is increased in the 0-6 month period post-PCI [18]. All patients were prospectively followed-up for adverse clinical events.

Socio-demographic and clinical characteristics

Socio-demographic variables included gender and age. Clinical variables were obtained from patients' medical records at the time of the index-PCI and included BMI (i.e., weight in kilograms divided by the square of the height in meters), type of stent (SES vs. BMS implantation), multi-vessel disease (multi-vessel disease vs. single-vessel disease/no vessel disease), indication for PCI (stable angina/silent ischemia, unstable angina, or myocardial infarction (MI)), cardiac history (i.e., previous MI, coronary artery bypass graft (CABG) surgery, or PCI), CAD risk factors (i.e., hypertension, hypercholesterolemia, diabetes mellitus, family history of CAD, and self-reported smoking) and prescribed cardiac discharge medications (i.e., ACE-inhibitors, beta-blockers, calcium-antagonists diuretics, oral nitrates, and statins). Information on clinical variables was prospectively collected at the time of the index-PCI and recorded in the institutional database.

Health status

Health status was assessed at baseline, 12, and 36 months post-PCI, using the 36-item Short-Form Health Survey (SF-36) [19]. The SF-36 consists of 36 items that contribute to 8 health status domains (i.e., physical functioning, role physical functioning, role emotional functioning, mental health, vitality, social functioning, bodily pain, and general health). Scale scores are obtained by summing the items together within a domain, dividing this outcome by the range of scores, and then transforming the raw scores to a scale from 0 to 100 [19]. A higher score on the SF-36 subdomains represents better functioning. A high score on the bodily pain scale indicates freedom from pain. The scale has good reliability with Cronbach's alpha ranging from .65 to .96 for all subscales [20].

Endpoint

The primary endpoint was defined as all-cause mortality. Deaths (n=54) occurring between PCI and psychological assessment were excluded as an endpoint from the analyses. Information on survival status was obtained from the Municipal Civil Registries

in May 2009. The median follow-up period for all-cause mortality was 7.0±1.7 years (range [.8-9.4 years]). Information on survival status at follow-up was complete for 1007 patients (98.8%).

Informed consent

The study protocol was approved by the medical ethics committee of the Erasmus MC, Rotterdam, and conducted according to the Helsinki Declaration [21]. Every patient provided informed consent.

Statistical analyses

Prior to statistical analyses, we dichotomized all 8 health status domains, as suggested by others, in order to enhance clinical interpretability [22, 23]. The lowest tertile was used to indicate poor health status and the 2 highest tertiles to indicate good health status. Categorization of BMI was adopted from the World Health Organization and defined as normal weight (18.5 to 24.9 kg/m^2), overweight (25 to 29.9 kg/m^2), and obese (≥30 kg/m^2) [24, 25]. For all analyses, normal weight was used as the reference group.

Group differences were examined using the Chi-square test (Fisher's exact test if appropriate) for nominal variables, while one-way ANOVA was used for continuous variables. Cumulative survival curves for BMI classes were constructed using the Kaplan-Meier method. The log-rank test was used to compare cumulative survival curves between groups. Univariable and multivariable Cox regression models were used to examine the effect of BMI on all-cause mortality. Covariates were entered into the model using the Enter method, thereby reducing the risk of overfitting [26]. In multivariable analysis, we adjusted for socio-demographic and clinical characteristics (i.e., gender, age, type of stent, multi-vessel disease, indication for PCI, cardiac history, CAD risk factors, and prescribed cardiac medications). Covariates were selected a priori based on the literature [10, 11, 27-29]. Health status was added to the final model to examine the role of health status in explaining the obesity paradox.

Hazard Ratios (HRs) with their corresponding 95% CIs were reported for Cox regression analyses. All results were based on 2-tailed tests and a *p*-value <.05 was used to indicate statistical significance. All statistical analyses were performed using SPSS for Windows 17.0 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Patient characteristics

Of 1675 eligible patients treated with PCI in the study period, 54 patients died within 6 months. Of the remaining 1621 patients asked to participate in the study, 602 did not return the questionnaire at baseline (62.9% response rate). Final analyses were based on data from 1019 patients (72.5% men; mean age 62.0±11.2 years, range [27-90] years). No systematic differences between participants and non-participants were found on baseline characteristics, except for non-participants more often having diabetes mellitus as compared with participants (21.0% vs. 14.8%, $p<.05$).

In the current sample, the prevalence of normal weight was 34.7% (354/1019), overweight was found in 45.9% (468/1019) of patients, whereas 19.3% (197/1019) was obese. At follow-up, 163 deaths (16.0%) from any cause were recorded. Patient baseline characteristics stratified by the 3 BMI categories are presented in Table 1. Overweight and obese patients were more likely to be younger as compared with the reference BMI group. Furthermore, obese patients were more likely to be female, smoke, have diabetes mellitus, and be prescribed diuretics.

BMI and all-cause mortality

The incidence of all-cause mortality at follow-up was 7.1% (72/1019) in the normal weight group versus 6.3% (64/1019) in the overweight group and 3.0% (31/1019) in the obesity group. Cumulative hazard functions differed significantly for the obese and overweight group as compared to the normal weight group (log-rank $X^2=6.59$, $p<.05$). In univariable Cox regression analysis, overweight was significantly associated with a cumulative decreased risk for all-cause mortality (HR=.71; 95%CI [.51-.97], $p=.030$), whereas obesity was not (HR=.96; 95%CI [.64-1.42], $p=.82$) (Figure 1). After adjusting for socio-demographic and clinical characteristics, overweight remained associated with a lower risk for all-cause mortality (HR=.60; 95%CI [.42-.86], $p=.005$), whereas no association was found between obesity and mortality (HR=.87; 95%CI [.55-1.37], $p=.55$) (Table 2).

BMI, all-cause mortality, and health status

In a final model, each of the 8 health status subdomains was added to the multivariable Cox regression analysis. After adjusting for socio-demographic and clinical characteristics, and the health status subdomains, the association between overweight and mortality remained unchanged (Table 2).

Table 1. Patient characteristics for the total sample and stratified by BMI classes [a]

	Total sample (N=1019)	***Normal weight (n=354)***	***Overweight (n=468)***	***Obesity (n=197)***	***p***
Socio-demographic characteristics					
Male gender	72	70	76	68	.005**
Age, mean (SD)	62 (11.2)	63 (11.4)	63 (11.2)	60 (10.6)	.005**
Clinical characteristics					
Multi-vessel disease	54	52	57	53	.44
Cardiac history [b]	59	57	59	61	.71
Indication for PCI					.66
Stable angina/ Silent ischemia	51	51	50	55	
Unstable angina	37	36	39	34	
MI	12	13	12	11	
Hypertension	29	32	28	25	.24
Hypercholesterolemia	59	56	59	61	.45
Diabetes mellitus	15	10	16	24	<.001***
Family history of CAD	15	14	15	17	.60
Self-reported smoking	42	35	42	54	<.001***
BMI, mean (SD)	27 (5.1)	23 (1.4)	27 (1.4)	34 (7.1)	<.001***
Cardiac medication					
Aspirin	95	94	95	95	.87
ACE-inhibitors	33	31	33	38	.20
Beta-blockers	67	66	67	68	.88
Calcium-antagonists	51	51	50	55	.54
Diuretics	15	12	15	22	.008**
Oral nitrates	17	18	15	19	.41
Statins	73	73	73	72	.96

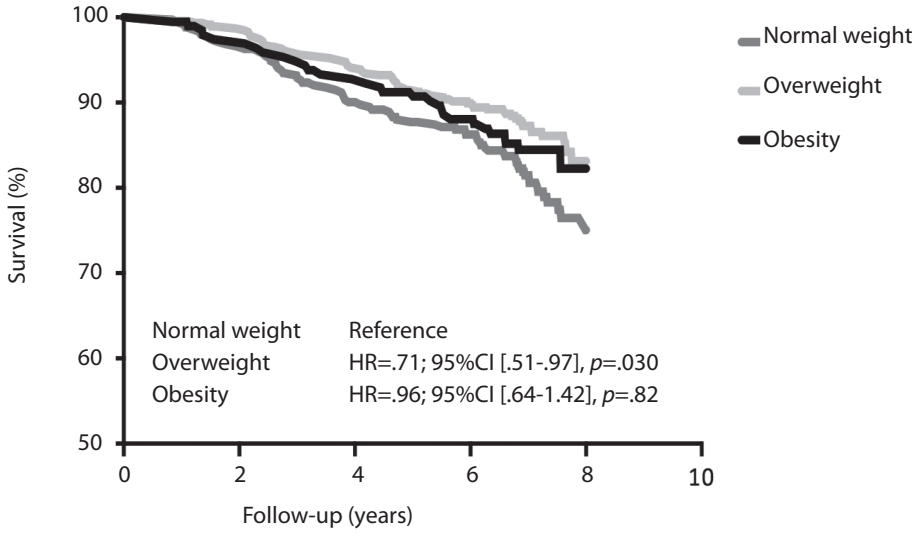
*$p \leq .05$; ** $p \leq .01$; *** $p \leq .001$

[a] Results are presented as % unless otherwise stated

[b] Previous myocardial infarction (MI), percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG) surgery

ACE = angiotensin-converting enzyme, BMI = body mass index (kg/m^2), CAD = coronary artery disease

Figure 1. Survival function stratified by BMI (unadjusted analysis)



Patients at risk (n)

Normal weight	341	318	305	282
Overweight	461	440	421	405
Obesity	191	182	173	166

Table 2. Association between BMI, health status, and all-cause mortality (adjusted analyses [a])

	HR	95%CI	*p*
BMI (without SF-36 subdomains)			
18.5 – 24.9	Reference		
25.0 – 29.9	.60	.42 - .86	.005**
≥30.0	.87	.55 – 1.37	.55
BMI (including SF-36 subdomains)			
Physical functioning			
18.5 – 24.9	Reference		
25.0 – 29.9	.59	.41 – .86	.005**
≥30.0	.78	.78 – 1.25	.30
Social functioning			
18.5 – 24.9	Reference		
25.0 – 29.9	.62	.43 – .89	.009**
≥30.0	.85	.54 – 1.34	.49
Role physical functioning			
18.5 – 24.9	Reference		
25.0 – 29.9	.64	.44 – .94	.024*
≥30.0	.89	.55 – 1.43	.63
Role emotional functioning			
18.5 – 24.9	Reference		
25.0 – 29.9	.62	.42 – .91	.015*
≥30.0	.88	.54 – 1.41	.59
Mental health			
18.5 – 24.9	Reference		
25.0 – 29.9	.59	.41 – .85	.005**
≥30.0	.87	.55 – 1.38	.56
Vitality			
18.5 – 24.9	Reference		
25.0 – 29.9	.57	.39 – .82	.003**
≥30.0	.84	.53 – 1.33	.46

Table 2. *Continued*

	HR	95%CI	*p*
Bodily pain			
18.5 – 24.9	Reference		
25.0 – 29.9	.62	.43 – .88	.008**
≥30.0	.80	.51 – 1.27	.35
General health			
18.5 – 24.9	Reference		
25.0 – 29.9	.62	.43 – .89	.010**
≥30.0	.82	.51 – 1.32	.41

*$p \leq .05$; ** $p \leq .01$; *** $p \leq .001$

[a] Adjusted for: Gender, age, hypercholesterolemia, hypertension, diabetes mellitus, smoking, family history of CAD, cardiac history, indication for PCI, multi-vessel disease, type of stent, aspirin, ACE-inhibitors, beta-blockers, calcium antagonists, diuretics, oral nitrates, and statins

BMI = body mass index (kg/m^2), SF-36 = 36-item Short-Form Health Survey

DISCUSSION

To our knowledge, this is the first study which examined whether the paradoxical association between BMI and mortality could be explained by health status. After a median follow-up of 7 years, overweight but not obesity was associated with a lower risk for all-cause mortality in patients treated with PCI, after adjusting for socio-demographic and clinical characteristics. We found no evidence that health status played a role in explaining the obesity paradox.

The results of the current study are in line with previous studies, demonstrating that overweight was associated with a decrease in mortality risk. A large meta-analysis conducted by Romero-Corral et al. [30] selected 40 studies with a total of 250.152 patients who underwent either PCI or CABG surgery. Results showed that overweight was associated with the lowest risk for total and cardiovascular mortality as compared with normal weight. In contrast to our findings, mildly obese patients also had lower mortality rates as compared with the normal weight group. Several other studies investigated the relationship between BMI and mortality. Most of them consistently showed an "obesity paradox" after PCI, with better survival in obese patients [5, 6, 9, 31, 32]. However, in our PCI cohort, only overweight but not obesity was associated with lower all-cause mortality as compared with patients with a normal weight. These discrepancies may possibly be attributed to bigger sample sizes (ranging from 2.099 up to 95.435 PCI patients) [5, 6, 9, 31, 32]

or differences in the follow-up duration, as the follow-up duration in previous studies was mainly limited to 1 year [5, 9].

In an attempt to explain the obesity paradox, previous studies in cardiac patients have mainly focused on medical factors, but results are inconclusive. For example, some studies examined the possible influence of guideline-based medications. These studies argued that higher BMI is associated with increased use of guideline-based medications, such as aspirin, beta-blockers, statins, and renin-angiotensin antagonists during hospitalization and at discharge. Hence, overweight and obese patients may receive more optimal medical treatment, which might contribute to improved long-term outcomes [2, 9]. Further, more severe hypercholesterolemia and higher levels of serum low-density lipoproteins in obese patients have been examined as potential explanations for the obesity paradox [33]. Other mechanisms like plasma renin levels, increased release of inflammatory cytokines, adinopectin secretion, and physical well-being could also be part of the explanation [34-37]. However, there is still not a clear understanding of the obesity paradox.

As previously shown, health status is an important outcome measure in CAD. Schenkeveld et al. [11] showed that poor health status is associated with adverse outcomes after PCI. Moreover, a recent meta-analysis showed that poor health status is associated with higher all-cause and cardiac mortality in CAD patients [10]. These findings were confirmed in other studies in patients undergoing cardiac intervention or surgery [38-40]. Several studies focused on the relation between BMI and health status, with most of them showing a negative relationship [12-15, 27, 41]. However, these studies were mainly focusing on heart failure patients [12], maintenance hemodialysis patients [15, 41], or the general population [13], but not PCI patients. These studies did not examine the role of health status as a possible explanation of the obesity paradox either.

The present study did not find evidence for health status as a possible explanation of the obesity paradox. There are some mechanisms which could be of importance in explaining our results. First, health status is probably a modifiable risk factor. Several mechanisms might be responsible for a connection between adverse clinical outcome and poor health status (i.e., demographic, physiological, and biomechanical mechanisms). Second, health status not only differs by level of obesity, but also by gender and age [13]. However, we adjusted for these factors in our multivariable models and no changes were observed. Finally, weight loss could result in significant improvements in health status, as measured with the SF-36 and the Kellner Symptom Questionnaire [42-44]. Future studies are warranted to more precisely investigate the complex nature of the obesity paradox and the factors that could play a role in explaining the paradox, taking socio-demographic, clinical, and psychological factors into account.

Limitations

Limitations of the current study must be acknowledged. First, data on abdominal obesity, as measured by waist circumference and waist/hip ratio, was not available. A recent meta-analysis showed that central obesity was associated with higher mortality in CAD, whereas total obesity (BMI) was not [45]. Therefore, future research should focus on the different aspects of obesity rather than total obesity alone. Second, the SF-36 is a generic measure of health status, which may be less sensitive to tap into patients' health status than the disease-specific measures used in previous studies [10]. Third, we only included patients who returned the SF-36 questionnaire. This might have influenced our results. Finally, our study population was not sufficiently large to perform subgroup analyses for extreme BMI's (i.e., ≤20 and ≥40). Therefore, we cannot deduce if our results show similar trends in these groups.

Conclusion

The current study showed that after a median follow-up of 7 years, overweight but not obesity was associated with lower mortality. In the current study health status did not seem to play a role in explaining the obesity paradox.

ACKNOWLEDGEMENTS

The authors of the manuscript have certified that they comply with the principles of ethical publishing in the International journal of Cardiology [46].

REFERENCES

1. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. J Am Med Assoc. 2012;307(5):491-7.
2. Steinberg BA, Cannon CP, Hernandez AF, Pan W, Peterson ED, Fonarow GC. Medical therapies and invasive treatments for coronary artery disease by body mass: The "obesity paradox" in the Get With The Guidelines database. Am J Cardiol. 2007;100(9):1331-5.
3. McGee DL. Body mass index and mortality: A meta-analysis based on person-level data from twenty-six observational studies. Ann Epidemiol. 2005;15(2):87-97.
4. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: Risk factor, paradox, and impact of weight loss. J Am Coll Cardiol. 2009;53(21):1925-32.
5. Gurm HS, Brennan DM, Booth J, Tcheng JE, Lincoff AM, Topol EJ. Impact of body mass index on outcome after percutaneous coronary intervention (the obesity paradox). Am J Cardiol. 2002;90(1):42-5.
6. Gruberg L, Weissman NJ, Waksman R, Fuchs S, Deible R, Pinnow EE, et al. The impact of obesity on the short-term and long-term outcomes after percutaneous coronary intervention: The obesity paradox? J Am Coll Cardiol. 2002;39(4):578-84.
7. Gruberg L, Mercado N, Milo S, Boersma E, Disco C, van Es GA, et al. Impact of body mass index on the outcome of patients with multivessel disease randomized to either coronary artery bypass grafting or stenting in the ARTS trial: The obesity paradox II? Am J Cardiol. 2005;95(4):439-44.
8. Hastie CE, Padmanabhan S, Slack R, Pell AC, Oldroyd KG, Flapan AD, et al. Obesity paradox in a cohort of 4880 consecutive patients undergoing percutaneous coronary intervention. Eur Heart J. 2010;31(2):222-6.
9. Lancefield T, Clark DJ, Andrianopoulos N, Brennan AL, Reid CM, Johns J, et al. Is there an obesity paradox after percutaneous coronary intervention in the contemporary era? An analysis from a multicenter Australian registry. JACC Cardiovasc Interv. 2010;3(6):660-8.
10. Mommersteeg PMC, Denollet J, Spertus JA, Pedersen SS. Health status as a risk factor in cardiovascular disease: A systematic review of current evidence. Am Heart J. 2009;157(2):208-18.
11. Schenkeveld L, Pedersen SS, van Nierop JWI, Lenzen MJ, de Jaegere PPT, Serruys PW, et al. Health-related quality of life and long-term mortality in patients treated with percutaneous coronary intervention. Am Heart J. 2010;159(3):471-6.
12. Evangelista LS, Moser DK, Westlake C, Hamilton MA, Fonarow GC, Dracup K. Impact of obesity on quality of life and depression in patients with heart failure. Eur J Heart Fail. 2006;8(7):750-5.
13. Larsson U, Karlsson J, Sullivan M. Impact of overweight and obesity on health-related quality of life--A Swedish population study. Int J Obes Relat Metab Disord. 2002;26(3):417-24.
14. Poston WS, Haddock CK, Conard M, Spertus JA. Impact of obesity on disease-specific health status after percutaneous coronary intervention in coronary disease patients. Int J Obes Relat Metab Disord. 2004;28(8):1011-7.
15. Kalantar-Zadeh K, Kuwae N, Wu DY, Shantouf RS, Fouque D, Anker SD, et al. Associations of body fat and its changes over time with quality of life and prospective mortality in hemodialysis patients. Am J Clin Nutr. 2006;83(2):202-10.
16. Lemos PA, Lee C, Degertekin M, Saia F, Tanabe K, Arampatzis CA, et al. Early outcome after sirolimus-eluting stent implantation in patients with acute coronary syndromes: Insights from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. J Am Coll Cardiol. 2003;41(11):2093-9.
17. Lemos PA, Serruys PW, van Domburg RT, Saia F, Arampatzis CA, Hoye A, et al. Unrestricted utilization of sirolimus-eluting stents compared with conventional bare stent implantation in the "real world". Circulation. 2004;109(2):190-5.
18. Rumsfeld JS, Magid DJ, Plomondon ME, Sacks J, Henderson W, Hlatky MA, et al. Health-related quality of life after percutaneous coronary intervention versus coronary bypass surgery in high-risk patients with medically refractory ischemia. J Am Coll Cardiol. 2003;41(10):1732-8.

19. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473-83.
20. Smith HJ, Taylor R, Mitchell A. A comparison of four quality of life instruments in cardiac patients: SF-36, QLI, QLMI, and SEIQoL. Heart. 2000;84(4):390-4.
21. Goodyear MDE, Krleza-Jeric K, Lemmens T. The declaration of Helsinki. Br Med J. 2007;335(7621):624-5.
22. Rumsfeld JS, Magid DJ, Plomondon ME, Sales AE, Grunwald GK, Every NR, et al. History of depression, angina, and quality of life after acute coronary syndromes. Am Heart J. 2003;145(3):493-9.
23. Spertus JA, Jones P, McDonell M, Fan V, Fihn SD. Health status predicts long-term outcome in outpatients with coronary disease. Circulation. 2002;106(1):43-9.
24. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults--The evidence report. National Institutes of Health. Obes Res. 1998;6 Suppl 2:51S-209S.
25. Obesity: Preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser. 2000;894:i-xii, 1-253.
26. Babyak MA. What you see may not be what you get: A brief, nontechnical introduction to overfitting in regression-type models. Psychosom Med. 2004;66(3):411-21.
27. Oreopoulos A, Padwal R, McAlister FA, Ezekowitz J, Sharma AM, Kalantar-Zadeh K, et al. Association between obesity and health-related quality of life in patients with coronary artery disease. Int J Obes. 2010;34(9):1434-41.
28. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol. 1996;49(12):1373-9.
29. Freedland KE, Reese RL, Steinmeyer BC. Multivariable models in biobehavioral research. Psychosom Med. 2009;71(2):205-16.
30. Romero-Corral A, Montori VM, Somers VK, Korinek J, Thomas RJ, Allison TG, et al. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: A systematic review of cohort studies. Lancet. 2006;368(9536):666-78.
31. Byrne J, Spence MS, Fretz E, Mildenberger R, Chase A, Berry B, et al. Body mass index, periprocedural bleeding, and outcome following percutaneous coronary intervention (from the British Columbia Cardiac Registry). Am J Cardiol. 2009;103(4):507-11.
32. Minutello RM, Chou ET, Hong MK, Bergman G, Parikh M, Iacovone F, et al. Impact of body mass index on in-hospital outcomes following percutaneous coronary intervention (report from the New York State Angioplasty Registry). Am J Cardiol. 2004;93(10):1229-32.
33. Rauchhaus M, Clark AL, Doehner W, Davos C, Bolger A, Sharma R, et al. The relationship between cholesterol and survival in patients with chronic heart failure. J Am Coll Cardiol. 2003;42(11):1933-40.
34. Galal W, van Gestel YR, Hoeks SE, Sin DD, Winkel TA, Bax JJ, et al. The obesity paradox in patients with peripheral arterial disease. Chest. 2008;134(5):925-30.
35. McCarty MF. A paradox resolved: The postprandial model of insulin resistance explains why gynoid adiposity appears to be protective. Med Hypotheses. 2003;61(2):173-6.
36. Oreopoulos A, Padwal R, Kalantar-Zadeh K, Fonarow GC, Norris CM, McAlister FA. Body mass index and mortality in heart failure: A meta-analysis. Am Heart J. 2008;156(1):13-22.
37. Uretsky S, Messerli FH, Bangalore S, Champion A, Cooper-Dehoff RM, Zhou Q, et al. Obesity paradox in patients with hypertension and coronary artery disease. Am J Med. 2007;120(10):863-70.
38. Rumsfeld JS, MaWhinney S, McCarthy M, Jr., Shroyer AL, VillaNueva CB, O'Brien M, et al. Health-related quality of life as a predictor of mortality following coronary artery bypass graft surgery. Participants of the Department of Veterans Affairs Cooperative Study Group on Processes, Structures, and Outcomes of Care in Cardiac Surgery. J Am Med Assoc. 1999;281(14):1298-303.
39. Lenzen MJ, Scholte op Reimer WJ, Pedersen SS, Boersma E, Maier W, Widimsky P, et al. The additional value of patient-reported health status in predicting 1-year mortality after invasive coronary procedures: A report from the Euro Heart Survey on Coronary Revascularisation. Heart. 2007;93(3):339-44.

40. Koch CG, Li L, Lauer M, Sabik J, Starr NJ, Blackstone EH. Effect of functional health-related quality of life on long-term survival after cardiac surgery. Circulation. 2007;115(6):692-9.
41. Kalantar-Zadeh K, Kopple JD, Block G, Humphreys MH. Association among SF36 quality of life measures and nutrition, hospitalization, and mortality in hemodialysis. J Am Soc Nephrol. 2001;12(12):2797-806.
42. Lavie CJ, Milani RV. Effects of cardiac rehabilitation, exercise training, and weight reduction on exercise capacity, coronary risk factors, behavioral characteristics, and quality of life in obese coronary patients. Am J Cardiol. 1997;79(4):397-401.
43. Milani RV, Lavie CJ, Cassidy MM. Effects of cardiac rehabilitation and exercise training programs on depression in patients after major coronary events. Am Heart J. 1996;132(4):726-32.
44. Lavie CJ, Morshedi-Meibodi A, Milani RV. Impact of cardiac rehabilitation on coronary risk factors, inflammation, and the metabolic syndrome in obese coronary patients. J Cardiometab Syndr. 2008;3(3):136-40.
45. Coutinho T, Goel K, Correa de Sa D, Kragelund C, Kanaya AM, Zeller M, et al. Central obesity and survival in subjects with coronary artery disease: A systematic review of the literature and collaborative analysis with individual subject data. J Am Coll Cardiol. 2011;57(19):1877-86.
46. Coats AJ, Shewan LG. Statement on authorship and publishing ethics in the International Journal of Cardiology. Int J Cardiol. 2011;153(3):239-40.

CHAPTER 7

The distressed (Type D) personality mediates the relationship between remembered parenting and psychological distress in cardiac patients

Damen NL, Versteeg H, van Helmondt SJ, De Jaegere PP, van Geuns RM, Meine MM, van Domburg RT, Pedersen SS. Psychol Health. 2014;29(3):318-33.

ABSTRACT

Objective: Both the distressed (Type D) personality (i.e., the combination of negative affectivity and social inhibition traits) and dysfunctional parenting styles are associated with anxiety and depression. As parenting styles have been related to personality development, dysfunctional parenting styles may also be associated with Type D personality. We examined whether remembered parenting was associated with anxiety and depression in cardiac patients and whether Type D personality mediated this relationship.

Methods: Our sample comprised 435 patients treated with percutaneous coronary intervention (PCI) and 123 patients with congestive heart failure (CHF). Patients completed the Hospital Anxiety and Depression Scale (HADS), Type D Scale (DS14), and Remembered Relationship with Parents (RRP[10]) scale.

Results: Remembered parenting was significantly associated with higher anxiety and depression levels and with Type D personality. In multivariable linear regression analyses, Type D personality accounted for 25-29% of the variance in anxiety and 23-46% of the variance in depression, while remembered parenting was no longer significantly associated with these domains. Sobel tests and bootstrapping indicated that Type D personality mediated the relationship between remembered parenting and anxiety and depression.

Conclusion: Type D personality mediated the relationship between remembered parenting and anxiety and depression in both PCI and CHF patients.

INTRODUCTION

The distressed (Type D) personality (i.e., the combination of negative affectivity and social inhibition traits) is a risk factor for anxiety and depression [1-4], poor health status and quality of life [5-7], and morbidity and mortality in patients with cardiovascular disease [8-11], as also confirmed in recent meta-analyses [12, 13]. Type D individuals experience a broad range of negative emotions and tend to inhibit these emotions in social interaction [14, 15].

Several links have been identified that may explain the association between Type D personality and adverse health outcomes in cardiac patients, and include both behavioral and biological pathways. Type D patients are less likely to engage in optimal health-related behaviors, such as exercising and quitting smoking [14, 16, 17], and are also less likely to consult their health care provider despite worrying more about their symptoms [18]. Biological pathways include immune activation [19, 20], dysfunctional stress reactivity [21, 22], and disturbances in cortisol regulation [23, 24].

However, knowledge of the mechanisms involved in the development of Type D personality itself is largely lacking. A recent study suggested that the characteristics of Type D personality may in part be attributed to genetic factors, as the heritability for Type D was found to be 52% [25]. Regarding environmental factors, remembered parenting may be of importance, as dysfunctional parenting styles, like overprotection or coldness, have been related to neuroticism [26-28], negative affectivity [29], and adult shyness [29]. These personality traits are closely related to the 2 core components of the Type D construct.

In addition, previous studies have indicated that dysfunctional parenting styles are associated with an increased risk for anxiety and depression [30-34]. Furthermore, dysfunctional parenting styles have been related to cardiovascular outcomes. Results from the Adverse Childhood Experiences (ACE) study showed that adverse childhood experiences, including household dysfunction, neglect, and abuse, are related to an increased risk for ischemic heart disease [35, 36]. Another study with a 35-year follow-up showed that dysfunctional parenting styles were associated with an increased risk for incident coronary artery disease (CAD) [37].

Because both Type D personality and dysfunctional parenting styles are related to psychological distress and dysfunctional parenting styles may also be associated with Type D personality, Type D may mediate the relationship between remembered dysfunctional parenting and anxiety and depression. Personality factors, such as self-esteem, emotional stability, and self-discipline, have been investigated as a mediating mechanism in the relationship between dysfunctional parenting styles and depression [38-40]. In a recent population-based study, Type D mediated the relationship between remembered parenting and perceived health [41], whereas another study demonstrated the mediating role of Type D in the relationship between attachment style and self-esteem [42].

Although both dysfunctional parenting styles and Type D personality have been related to adverse cardiovascular outcomes, to date no study examined this mediation model in cardiac patients. Hence, the aim of the current study was to examine whether remembered parenting is associated with anxiety and depression in cardiac patients, and whether Type D personality mediates this relationship. To examine whether the effects differ between stages of heart disease, we used 2 cohorts of cardiac patients, patients treated with percutaneous coronary intervention (PCI) and congestive heart failure (CHF) patients.

METHODS

Participants and procedure

The study sample included 558 cardiac patients. The first cohort comprised 435 consecutive patients treated with percutaneous coronary intervention (PCI) to reflect early-stage heart disease. Patients were treated with PCI between February 2, 2006 and September 14, 2006 at the Erasmus MC, Rotterdam, the Netherlands. In all patients, the paclitaxel-eluting stent (PES) was used as the default strategy. No exclusion criteria were applied and all PCI patients were eligible for enrolment regardless of their anatomical, clinical, or psychological presentation. One month post-PCI, patients were asked to complete a set of standardized and validated psychological questionnaires, as preliminary evidence suggests that psychological assessment at the time of the index-PCI may be less optimal than 1 month post-procedure [43].

To represent end-stage heart disease, the second cohort comprised 123 patients receiving a first-time cardiac resynchronization therapy defibrillator (CRT-D) between January 21, 2009 and August 9, 2010 at the University Medical Center Utrecht (UMCU), the Netherlands. All patients participated in the ongoing "The influence of PSYchological factors on health outcomes in HEART failure patients treated with CRT: A prospective, single-center, observational study (PSYHEART-CRT)". The PSYHEART-CRT study was primarily designed to examine whether psychological factors moderate the effect of objectively assessed CRT response on patient-reported outcomes in CHF patients. Exclusion criteria were age <18 or >85 years, a history of psychiatric illness other than affective/anxiety disorders, cognitive impairments (e.g., dementia), on the waiting list for heart transplantation, and insufficient knowledge of the Dutch language. We did not exclude patients with a history of affective/anxiety disorders, as we were particularly interested in patients with increased levels of depression and anxiety, irrespective of the fact if this had been diagnosed as a disorder. One day prior to implantation, patients were asked to complete a set of standardized and validated psychological questionnaires.

The current study was approved by the medical ethics committee of the respective hospitals and was conducted in accordance with the Helsinki Declaration [44]. All patients provided informed consent.

Measures

Socio-demographic and clinical characteristics of PCI patients

Socio-demographic characteristics included gender and age. Clinical characteristics included multi-vessel disease (multi-vessel disease vs. single-vessel disease/no vessel disease), body mass index (BMI), cardiac history (i.e., previous myocardial infarction (MI), coronary artery bypass graft (CABG) surgery, or PCI), indication for PCI (stable angina/silent ischemia, unstable angina, or MI), CAD risk factors (i.e., hypertension, diabetes mellitus, family history of CAD, and self-reported smoking), and prescribed cardiac discharge medications (i.e., aspirin, ACE-inhibitors, beta-blockers, calcium-antagonists, diuretics, oral nitrates, and statins). Information on socio-demographic and clinical characteristics was obtained from patients' medical records.

Socio-demographic and clinical characteristics of CHF patients

Socio-demographic characteristics included gender and age. Clinical characteristics included etiology (ischemic vs. non-ischemic), implantable cardioverter defibrillator (ICD) indication (primary vs. secondary prevention), New York Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF), BMI, cardiac history (i.e., previous MI, CABG, or PCI), smoking, and prescribed cardiac medications at hospital admission for CRT-D implantation. Information on socio-demographic and clinical characteristics was obtained from patients' medical records.

Type D personality

In both cohorts, Type D personality was assessed with the 14-item Type D scale (DS14) that comprises 2 subscales, negative affectivity (NA) (e.g., "I often feel unhappy") and social inhibition (SI) (e.g., "I am a closed kind of person"), each consisting of 7 items. Items are scored on a 5-point Likert scale ranging from 0 ("false") to 4 ("true"). Based on findings from the Item Response Theory [45], a standardized cut-off score ≥10 on both subscales is used to identify individuals with a Type D personality. However, previous studies indicated that Type D personality is better represented as a continuous construct [46] and could be derived from the interaction effect of the NA and SI subscales [24, 47]. In the current study, we used this interaction term as a continuous measure of Type D personality in all analyses. In the cohort of PCI patients, Cronbach's alpha was .86 for NA and .85 for SI, whereas in the cohort of CHF patients, Cronbach's alpha was .90 for NA and .87 for SI.

Anxiety and depression

All patients completed the Dutch version of the Hospital Anxiety and Depression Scale (HADS) to assess symptoms of anxiety and depression [48, 49]. Both subscales consist of 7 items that are answered on a 4-point Likert scale ranging from 0 to 3 [48]. The HADS has demonstrated to be a valid screening tool for detecting symptoms of anxiety and depression [50, 51], and has been shown to predict mortality in patients referred for exercise testing [52]. The internal consistency has been demonstrated previously, with Cronbach's alpha of .83 for the anxiety subscale (HADS-A) and .82 for the depression subscale (HADS-D) [50]. In the current study, in the cohort of PCI patients Cronbach's alpha was .85 for HADS-A and .81 for HADS-D, whereas in the cohort of CHF patients, Cronbach's alpha was .83 for HADS-A and .82 for HADS-D.

Remembered parenting

The Remembered Relationship with Parents (RRP[10]) scale was used to retrospectively assess perceptions of parental care [34]. This self-report instrument assesses caregiving processes with an emphasis on deficiencies in emphatic relationships between parents and child. Respondents are asked to describe the relationship with their parents while growing up on a 5-point Likert scale ranging from 0 ("false") to 4 ("true"). The RRP[10] consists of 2 subscales, alienation from parents and control by parents. Alienation refers to respondents' perception of dysfunctional communication and intimacy with their parents (e.g., "I often felt that my parents did not understand me"), while control refers to the respondent's perception of an overprotective parenting style (e.g., "I wished my parents would worry less about me"). Remembered alienation and control were assessed with reference to the father and mother separately. However, in the current study the combined score of both parents was used to assess alienation and control (score range [0-40]). A higher score on both parenting scales indicates worse remembered parenting while growing up. Because of the non-pathological focus, the RRP[10] is suitable for use in non-psychiatric populations and in epidemiological and clinical research [41]. The RRP[10] has a good factor structure, internal consistency (Cronbach's alpha = .83-.86), and convergent validity with the Parenting Bonding Instrument (PBI) [34, 41, 53]. In the current study, in the cohort of PCI patients Cronbach's alpha was .90, whereas in the cohort of CHF patients, Cronbach's alpha was .89.

Statistical analyses

Before investigating whether Type D personality, as represented by the interaction term of NA and SI, mediated the relationship between remembered parenting and anxiety and depression, we examined whether the assumptions underlying the mediation model according to Baron and Kenny [54] were fulfilled: 1) remembered parenting had to be related

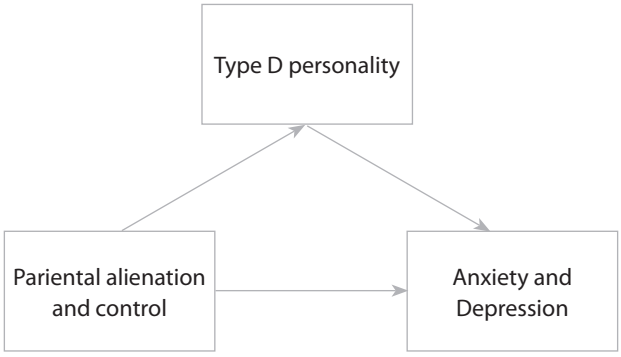
to anxiety and depression, 2) remembered parenting had to be associated with the mediator Type D personality, and 3) Type D personality had to be associated with anxiety and depression, after adjusting for remembered parenting (Figure 1). Type D personality was considered a mediator if it accounted for a significant part of the relation between remembered parenting and anxiety and depression [54]. The assumptions for mediation were tested with a series of linear regression models. In general, with mediation we meant to state that the direct effect of remembered parenting on psychological distress might be weakened by an indirect effect via Type D personality.

To allow for a more direct test of the mediation effect, Sobel tests were used [55]. Sobel tests, which are products of coefficient tests for the mediating variable effect, are used to test the significance of the mediating variable effect by dividing the estimate of the mediating variable effect by its standard error and comparing this value to a standard normal distribution. In contrast with causal step methods (e.g., the Baron and Kenny approach), Sobel tests are less prone to Type I errors and have more statistical power to detect mediation if present [56]. To further test the robustness of our mediation model, bootstrapping, using 5000 sample replicates, was performed [57]. Bootstrapping is especially suitable for small sample sizes and avoids the assumption that the indirect effects are normally distributed. Indirect effects are unstandardized coefficients, which are significant when the 95% confident interval does not contain zero.

In additional multivariable linear regression analyses, we examined whether Type D personality remained significantly associated with anxiety and depression, after adjusting for socio-demographic and clinical variables. In the PCI cohort, we adjusted for all baseline characteristics listed in Table 1, except for aspirin as almost all patients (i.e., 95%) were prescribed aspirin. In the CHF cohort, we adjusted for gender, age, NYHA functional class, LVEF, etiology, and diabetes mellitus. Covariates were selected a priori based on the literature [58-60]. The assumption of multicollinearity was checked for all separate multivariable linear regression models.

Sobel tests and bootstrapping were performed with SPSS macros by Preacher and Hayes [57, 61] (http://www.afhayes.com/spss-sas-and-mplus-macros-and-code.html), as SPSS does not provide the possibility to directly test the mediation effect. For all other analyses, SPSS for Windows version 17.0 was used.

Figure 1. Mediation model for parental alienation and control, Type D personality, and anxiety and depression



RESULTS

Characteristics of PCI patients

Of the 869 eligible patients treated with PCI in the study period, 29 died within 4 weeks. The remaining 840 were asked to participate in the study, of which 297 did not return the questionnaire at baseline (64.6% response rate). Of the remaining 543 patients, 108 did not complete the HADS, DS14, or RRP[10]. Final analyses were based on data from 435 patients (77.5% men; mean age 62.6±10.7 years, range [30-91] years). In the current study, the mean scores for NA and SI were 8.2±6.2 and 9.1±6.4, respectively. Patient characteristics for the total sample of PCI patients are presented in Table 1.

Characteristics of CHF patients

Of the 182 eligible patients implanted with a CRT-D in the study period, 35 refused to participate and 8 patients did not return the questionnaire at baseline (76.4% response rate). Of the remaining 139 patients, 16 did not complete the HADS, DS14, or RPP[10]. Final analyses were based on 123 patients (71.5% men; mean age 65.3±10.5 years, range [30-84] years). In the current study, the mean scores for NA and SI were 8.4±6.4 and 9.1±5.8, respectively. Patient characteristics for the total sample of CHF patients are presented in Table 1.

Table 1. Patient characteristics for the total sample [a]

	PCI patients (N=435)	***CHF patients (N=123)***
Socio-demographic characteristics		
Male gender	336 (77.4)	88 (71.5)
Age, mean (SD)	62.6 (10.7)	65.3 (10.5)
Clinical characteristics		
Cardiac history [b]	164 (38.5)	59 (48.4)
Hypertension	208 (53.1)	47 (38.2)
Diabetes mellitus	76 (17.5)	24 (19.5)
Self-reported smoking	114 (29.1)	17 (13.8)
BMI, mean (SD)	27.3 (3.9)	27.3 (5.5)
Multi-vessel disease	221 (51.0)	-
Family history of CAD	208 (53.1)	-
Indication for PCI		
Stable angina/ Silent ischemia	174 (40.7)	-
Unstable angina	110 (25.8)	-
MI	143 (33.5)	-
Ischemic etiology	-	64 (52.0)
CRT-D for primary prevention	-	98 (79.7)
NYHA functional class III or IV	-	99 (80.5)
LVEF, mean (SD)	-	24.6 (8.5)
Cardiac medication		
Aspirin	423 (97.7)	38 (30.9)
ACE-inhibitors	70 (16.2)	82 (66.7)
Beta-blockers	302 (69.7)	94 (76.4)
Calcium-antagonists	5 (1.2)	9 (7.3)
Diuretics	4 (.9)	105 (85.4)
Oral nitrates	61 (14.1)	21 (17.1)
Statins	362 (83.6)	74 (60.2)

[a] Results are presented as n (%) unless otherwise stated; [b] Previous myocardial infarction (MI), percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG) surgery; ACE = angiotensin-converting enzyme, BMI = body mass index (kg/m^2), CAD = coronary artery disease, CRT-D = cardiac resynchronization therapy defibrillator, LVEF = Left ventricular ejection fraction, NYHA = New York Heart Association

Type D, parenting, and distress in PCI patients

In PCI patients, we tested the hypothesis that Type D personality mediated the relationship between remembered parenting and anxiety and depression, using a series of linear regression analyses. Results indicated that parental alienation and control were associated with both more anxiety ($p<.001$) and depression ($p<.001$) (Table 2). The second assumption underlying the mediation model was also fulfilled: Parental alienation and control were significantly related to Type D personality ($p<.001$) (Table 2). Multivariable linear regression analyses showed that Type D personality was significantly associated with both higher anxiety ($p<.001$) and depression ($p<.001$), when adjusting for remembered alienation and control (Table 2). Once Type D personality was included in the model, the effect of the remembered relationship with parents on anxiety and depression was no longer significant, indicating mediation.

Sobel tests confirmed that Type D personality significantly mediated the relationship between remembered parenting and anxiety ($z'=7.58$, $p<.001$ for alienation and $z'=6.88$, $p<.001$ for control, respectively) and depression ($z'=7.20$, $p<.001$ for alienation and $z'=6.47$, $p<.001$ for control, respectively). In addition, bootstrapping further confirmed the mediation model with significant indirect effects of Type D personality on the relationship between remembered parenting and anxiety (indirect effect=.08, SE=.01, 95%CI [.06-.12] for alienation and indirect effect=.08, SE=.01, 95%CI [.06-.11] for control, respectively) and depression (indirect effect=.09, SE=.01, 95%CI [.06-.12] for alienation and indirect effect=.08, SE=.01, 95%CI [.06-.11] for control, respectively).

In extended multivariable linear regression analyses, Type D personality remained significantly associated with higher levels of anxiety and depression ($\beta=.56$, $p<.001$, $\Delta R^2=.26$ and $\beta=.54$, $p<.001$, $\Delta R^2=.24$, respectively), after adjusting for socio-demographic and clinical variables. Female gender ($\beta=.11$, $p=.002$) and diabetes mellitus ($\beta=.09$, $p=.038$) were associated with higher levels of anxiety, whereas higher age ($\beta=.12$, $p=.007$), diabetes mellitus ($\beta=.11$, $p=.020$), and smoking ($\beta=.12$, $p=.014$) were associated with higher levels of depression. In all multivariable linear regression models, the assumption of non-multicollinearity was met.

Type D, parenting, and distress in CHF patients

In CHF patients, parental alienation and control were significantly associated with more anxiety (p<.001) and depression (p<.01) (Table 2). Parental alienation and control were also significantly related to Type D personality (p<.001) (Table 2). Once again, Type D personality was significantly associated with both higher anxiety (p<.001) and depression (p<.001), when adjusting for parental alienation and control (Table 3). Once Type D personality was included in the model, the effect of remembered parenting on anxiety and depression was no longer significant, indicating mediation.

Sobel tests confirmed that Type D mediated the relationship between remembered parenting and anxiety (z=3.67, p<.001 for alienation and z=3.37, p<.001 for control, respectively) and depression (z=3.67, p<.001 for alienation and z=3.58, p<.001 for control, respectively). In addition, bootstrapping further confirmed the mediation model with significant indirect effects of Type D personality on the relationship between remembered parenting and anxiety (indirect effect=10, SE=.03, 95%CI [.05-.15] for alienation and indirect effect=.09, SE=.03, 95%CI [.04-16] for control, respectively) and depression (indirect effect=.11, SE=.02, 95%CI [.07-.16] for alienation and indirect effect=.11, SE=.04, 95%CI [.05-.18] for control, respectively).

In extended multivariable regression analyses, Type D personality remained significantly associated with higher levels of anxiety and depression (β=.45, p<.001, ΔR^2=.16 and β=.57, p<.001, ΔR^2=.26, respectively), after adjusting for remembered parenting, age, gender, NYHA functional class, LVEF, etiology, and diabetes. None of the socio-demographic and clinical variables were significantly associated with anxiety, whereas higher NYHA functional class was associated with higher levels of depression (β=.25, p=.002). In all multivariable linear regression models, the assumption of non-multicollinearity was met.

Table 2. Associations between parental alienation and control, anxiety and depression, and Type D personality (assumptions 1 and 2)

	PCI patients									CHF patients								
	Anxiety			Depression			Type D personality			Anxiety			Depression			Type D personality		
	β	*p*	R^2	β	*p*	R^2	β	*p*	R^2	β	*p*	R^2	β	*p*	R^2	β	*p*	R^2
Parental alienation	.22	<.001	.05	.19	<.001	.03	.38	<.001	.15	.33	<.001	.10	.32	<.001	.10	.37	<.001	.13
Parental control	.27	<.001	.07	.25	<.001	.06	.35	<.001	.12	.30	.001	.08	.24	.009	.05	.33	<.001	.10

R^2 for the full model

Table 3. Associations between Type D personality and anxiety and depression, adjusted for parental alienation and control (assumption 3)

	PCI patients						CHF patients					
	Anxiety			Depression			Anxiety			Depression		
	β	*p*	ΔR^2	β	*p*	ΔR^2	β	*p*	ΔR^2	β	*p*	ΔR^2
Type D personality	.59	<.001	.29	.55	<.001	.26	.54	<.001	.25	.66	<.001	.46
Parental alienation	-.006	.89	-.002	-.02	.68	-.001	.12	.12	.01	.08	.27	.001
Type D personality	.56	<.001	.28	.52	<.001	.23	.55	<.001	.27	.69	<.001	.46
Parental control	.08	.064	.004	.07	.10	.003	.12	.13	.008	.01	.91	-.05

ΔR^2 compared to the model including all other variables

DISCUSSION

To our knowledge, this is the first study to report on the role of Type D personality as a mediator between remembered parenting and anxiety and depression in cardiac patients. In both PCI and CHF patients, remembered dysfunctional parenting was significantly associated with higher anxiety and depression levels as well as with Type D personality. In multivariable linear regression analyses, Type D personality accounted for 25-29% of the variance in anxiety and 23-46% of the variance in depression, while remembered parenting was no longer significantly associated with any of these symptoms. Sobel tests and bootstrapping confirmed the finding that Type D personality mediated the relationship between remembered parenting and anxiety and depression in both PCI and CHF patients.

The current study corroborates the findings of previous studies, demonstrating that personality factors may mediate the relationship between parenting styles and depression [38-40]. In line with a recent study in the general Dutch population, we found that Type D personality mediated the relationship between remembered parenting and psychological distress [41]. However, the current study extends previous research by showing that this mediation model is also applicable to cardiac patients.

A paucity of studies have examined the association between parenting styles and personality development, showing that dysfunctional parenting styles, like overprotection and coldness, are related to the development of for example neuroticism [26-28] and negative affectivity [29]. This is the first study to show that there is a link between remembered parenting and Type D personality in cardiac patients, with Type D patients reporting significantly more alienation from and control by parents than non-Type D patients. Given that Type D personality has been associated with a 2-fold increased risk for poor physical and mental health status and a more than 3-fold increased risk for poor prognosis in CAD [12, 13], future longitudinal studies are warranted to examine whether dysfunctional parenting styles may contribute to the development of Type D personality.

Information on genetic and environmental factors that contribute to the development of Type D personality is important for developing appropriate intervention trials that target this personality disposition in patients with established cardiovascular disease. To our knowledge, only one recent psychological intervention trial in Dutch community residents specifically targeted Type D personality. In this study, a mindfulness-based stress reduction intervention was designed to reduce the NA and SI characteristics of Type D personality. After the 8-week intervention, the intervention group showed a significant decrease in both NA and SI dimensions, although change in Type D caseness did not differ between groups [62]. In post-MI patients, a psychological intervention trial has been planned to evaluate the effect of short-term psychotherapy on incident CAD

and levels of psychological distress, including Type D personality [63]. Results of the current study suggest that when designing a behavioral intervention for Type D patients, it may also be important to take remembered parenting into account.

The limitations of the current study must be acknowledged. First, the cross-sectional study design does not allow for causal inferences about the relationship between remembered parenting, Type D personality, and anxiety and depression. A so-called recall bias may arise, as it is possible that childhood memories are influenced by the patient's personality and current feelings of distress. For example, given the high levels of SI in Type D patients, these patients may report that they feel more alienated from their parents as compared with patients with lower levels of SI. This should be investigated further. Second, patients who indicated that there was only maternal or paternal parenting were excluded from the analyses. This was the case in 7.7% (42/543) of PCI patients and 10.1% (14/139) of CHF patients. Third, data on Type D personality and anxiety and depression was obtained from self-report questionnaires and therefore, common method variance may have contributed to the significant results. However, we only used validated and reliable questionnaires to assess the psychological constructs studied, which have been used frequently in different cardiovascular patient groups [1, 64]. Finally, in contrast to the current study, previous studies mainly used the PBI to assess remembered parenting rather than the RRP[10]. However, it has been shown that the RRP[10] has good convergent validity with the PBI [34, 41, 53].

In conclusion, the current study showed that Type D personality mediated the relationship between remembered parenting and anxiety and depression in patients treated with PCI and CHF patients. Hence, in psychological intervention trials targeting Type D personality, it may be important to address remembered parenting. Future studies using a longitudinal design are warranted to examine the directionality of the relationship between remembered parenting, Type D personality, and psychological distress in cardiac patients.

ACKNOWLEDGEMENTS

This research was supported with a VIDI grant (91710393) to Prof. Susanne S. Pedersen from the Netherlands Organization for Health Research and Development (ZonMW), The Hague, the Netherlands.

REFERENCES

1. Pedersen SS, Ong ATL, Sonnenschein K, Serruys PW, Erdman RAM, van Domburg RT. Type D personality and diabetes predict the onset of depressive symptoms in patients after percutaneous coronary intervention. Am Heart J. 2006;151(2):367.e1-376.e6.
2. Pedersen SS, van Domburg RT, Theuns DAMJ, Jordaens L, Erdman RAM. Type D personality is associated with increased anxiety and depressive symptoms in patients with an implantable cardioverter defibrillator and their partners. Psychosom Med. 2004;66(5):714-9.
3. Spindler H, Pedersen SS, Serruys PW, Erdman RAM, van Domburg RT. Type-D personality predicts chronic anxiety following percutaneous coronary intervention in the drug-eluting stent era. J Affect Disord. 2007;99(1–3):173-9.
4. van Gestel YRBM, Pedersen SS, van de Sande M, de Jaegere PPT, Serruys PW, Erdman RAM, et al. Type-D personality and depressive symptoms predict anxiety 12 months post-percutaneous coronary intervention. J Affect Disord. 2007;103(1):197-203.
5. Schiffer AA, Pedersen SS, Widdershoven JW, Hendriks EH, Winter JB, Denollet J. The distressed (type D) personality is independently associated with impaired health status and increased depressive symptoms in chronic heart failure. Eur J Cardiovasc Prev Rehabil. 2005;12(4):341-6.
6. Pedersen SS, Denollet J, Ong ATL, Serruys PW, Erdman RAM, van Domburg RT. Impaired health status in Type D patients following PCI in the drug-eluting stent era. Int J Cardiol. 2007;114(3):358-65.
7. Mols F, Martens EJ, Denollet J. Type D personality and depressive symptoms are independent predictors of impaired health status following acute myocardial infarction. Heart. 2010;96(1):30-5.
8. Pedersen SS, Lemos PA, van Vooren PR, Liu TKK, Daemen J, Erdman RAM, et al. Type D personality predicts death or myocardial infarction after bare metal stent or sirolimus-eluting stent implantation: A Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry substudy. J Am Coll Cardiol. 2004;44(5):997-1001.
9. Denollet J, Pedersen SS, Vrints CJ, Conraads VM. Usefulness of Type D personality in predicting five-year cardiac events above and beyond concurrent symptoms of stress in patients with coronary heart disease. Am J Cardiol. 2006;97(7):970-3.
10. Pedersen SS, Denollet J, Ong AT, Sonnenschein K, Erdman RA, Serruys PW, et al. Adverse clinical events in patients treated with sirolimus-eluting stents: The impact of Type D personality. Eur J Cardiovasc Prev Rehabil. 2007;14(1):135-40.
11. Martens EJ, Mols F, Burg MM, Denollet J. Type D personality predicts clinical events after myocardial infarction, above and beyond disease severity and depression. J Clin Psychiatry. 2010;71(6):778-83.
12. Versteeg H, Spek V, Pedersen SS, Denollet J. Type D personality and health status in cardiovascular disease populations: A meta-analysis of prospective studies. Eur J Cardiovasc Prev Rehabil. 2011;19(6):1373-80.
13. Denollet J, Schiffer AA, Spek V. A general propensity to psychological distress affects cardiovascular outcomes. Circ Cardiovasc Qual Outcomes. 2010;3(5):546-57.
14. Pedersen SS, Denollet J. Is Type D personality here to stay? Emerging evidence across cardiovascular-disease patient groups. Curr Cardiol Rev. 2006;2(3):205-13.
15. Denollet J. DS14: Standard assessment of negative affectivity, social inhibition, and Type D personality. Psychosom Med. 2005;67(1):89-97.
16. Williams L, O'Connor RC, Grubb N, O'Carroll R. Type D personality predicts poor medication adherence in myocardial infarction patients. Psychol Health. 2011;26(6):703-12.
17. Steptoe A, Molloy GJ. Personality and heart disease. Heart. 2007;93(7):783-4.
18. Schiffer AA, Denollet J, Widdershoven JW, Hendriks EH, Smith ORF. Failure to consult for symptoms of heart failure in patients with a type-D personality. Heart. 2007;93(7):814-8.
19. Denollet J, Conraads VM, Brutsaert DL, de Clerck LS, Stevens WJ, Vrints CJ. Cytokines and immune activation in systolic heart failure: The role of Type D personality. Brain Behav Immun. 2003;17(4):304-9.

20. Conraads VM, Denollet J, De Clerck LS, Stevens WJ, Bridts C, Vrints CJ. Type D personality is associated with increased levels of tumour necrosis factor (TNF)-α and TNF-α receptors in chronic heart failure. Int J Cardiol. 2006;113(1):34-8.
21. Habra ME, Linden W, Anderson JC, Weinberg J. Type D personality is related to cardiovascular and neuroendocrine reactivity to acute stress. J Psychosom Res. 2003;55(3):235-45.
22. Williams L, O'Carroll RE, O'Connor RC. Type D personality and cardiac output in response to stress. Psychol Health. 2009;24(5):489-500.
23. Molloy GJ, Perkins-Porras L, Strike PC, Steptoe A. Type-D Personality and cortisol in survivors of acute coronary syndrome. Psychosom Med. 2008;70(8):863-8.
24. Whitehead DL, Perkins-Porras L, Strike PC, Magid K, Steptoe A. Cortisol awakening response is elevated in acute coronary syndrome patients with type-D personality. J Psychosom Res. 2007;62(4):419-25.
25. Kupper N, Boomsma DI, de Geus EJC, Denollet J, Willemsen G. Nine-year stability of Type D personality: Contributions of genes and environment. Psychosom Med. 2011;73(1):75-82.
26. Furukawa T. Perceived parental rearing, personality and mental status in Japanese adolescents. J Adolesc. 1992;15(3):317-22.
27. McCrae RR, Costa PT. Recalled parent-child relations and adult personality. J Pers. 1988;56(2):417-34.
28. Reti IM, Samuels JF, Eaton WW, Bienvenu OJ, Costa PT, Nestadt G. Influences of parenting on normal personality traits. Psychiatry Res. 2002;111(1):55-64.
29. Aron EN, Aron A, Davies KM. Adult shyness: The interaction of temperamental sensitivity and an adverse childhood environment. Pers Soc Psychol Bull. 2005;31(2):181-97.
30. Neale MC, Walters E, Heath AC, Kessler RC, Pérusse D, Eaves LJ, et al. Depression and parental bonding: Cause, consequence, or genetic covariance? Genet Epidemiol. 1994;11(6):503-22.
31. Lee A, Hankin BL. Insecure attachment, dysfunctional attitudes, and low self-esteem predicting prospective symptoms of depression and anxiety during adolescence. J Clin Child Adolesc Psychol. 2009;38(2):219-31.
32. Rapee RM. Potential role of childrearing practices in the development of anxiety and depression. Clin Psychol Rev. 1997;17(1):47-67.
33. Kendler KS, Myers J, Prescott CA. Parenting and adult mood, anxiety and substance use disorders in female twins: An epidemiological, multi-informant, retrospective study. Psychol Med. 2000;30(2):281-94.
34. Denollet J, Smolderen KGE, van den Broek KC, Pedersen SS. The 10-item Remembered Relationship with Parents (RRP10) scale: Two-factor model and association with adult depressive symptoms. J Affect Disord. 2007;100(1–3):179-89.
35. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: The Adverse Childhood Experiences (ACE) Study. Am J Prev Med. 1998;14(4):245-58.
36. Dong M, Giles WH, Felitti VJ, Dube SR, Williams JE, Chapman DP, et al. Insights into causal pathways for ischemic heart disease: Adverse childhood experiences study. Circulation. 2004;110(13):1761-6.
37. Russek LG, Schwartz GE. Perceptions of parental caring predict health status in midlife: A 35-year follow-up of the Harvard Mastery of Stress Study. Psychosom Med. 1997;59(2):144-9.
38. Avagianou P, Zafiropoulou M. Parental bonding and depression: Personality as a mediating factor. Int J Adolesc Med Health. 2008;20(3):261-9.
39. Enns MW, Cox BJ, Larsen DK. Perceptions of parental bonding and symptom severity in adults with depression: Mediation by personality dimensions. Can J Psychiatry. 2000;45(3):263-8.
40. Parker G. Parental rearing style: Examining for links with personality vulnerability factors for depression. Soc Psychiatry Psychiatr Epidemiol. 1993;28(3):97-100.
41. van den Broek KC, Smolderen KG, Pedersen SS, Denollet J. Type D personality mediates the relationship between remembered parenting and perceived health. Psychosomatics. 2010;51(3):216-24.
42. Huis in 't Veld EMJ, Vingerhoets AJJM, Denollet J. Attachment style and self-esteem: The mediating role of Type D personality. Pers Individ Dif. 2011;50(7):1099-103.

43. Poston WSC, Haddock CK, Conard MW, Jones P, Spertus J. Assessing depression in the cardiac patient. Behav Modif. 2003;27(1):26-36.
44. Goodyear MDE, Krleza-Jeric K, Lemmens T. The Declaration of Helsinki. BMJ. 2007;335(7621):624-5.
45. Emons WHM, Meijer RR, Denollet J. Negative affectivity and social inhibition in cardiovascular disease: Evaluating Type-D personality and its assessment using item response theory. J Psychosom Res. 2007;63(1):27-39.
46. Ferguson E, Williams L, O'Connor RC, Howard S, Hughes BM, Johnston DW, et al. A taxometric analysis of Type-D Personality. Psychosom Med. 2009;71(9):981-6.
47. Denollet J, Pedersen SS, Ong AT, Erdman RA, Serruys PW, van Domburg RT. Social inhibition modulates the effect of negative emotions on cardiac prognosis following percutaneous coronary intervention in the drug-eluting stent era. Eur Heart J. 2006;27(2):171-7.
48. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-70.
49. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med. 1997;27(2):363-70.
50. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res. 2002;52(2):69-77.
51. Herrmann C. International experiences with the Hospital Anxiety and Depression Scale - A review of validation data and clinical results. J Psychosom Res. 1997;42(1):17-41.
52. Herrmann C, Brand-Driehorst S, Buss U, Rüger U. Effects of anxiety and depression on 5-year mortality in 5057 patients referred for exercise testing. J Psychosom Res. 2000;48(4-5):455-62.
53. Parker G, Tupling H, Brown LB. A parental bonding instrument. Br J Med Psychol. 1979;52(1):1-10.
54. Baron R, Kenny D. The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. J Pers Soc Psychol. 1986;51(6):1173-82.
55. Sobel M. Asymptotic confidence intervals for indirect effects in structural equation models. Sociol Methodol. 1982;13:290-312.
56. MacKinnon D, Lockwood C, Hoffman J, West S, Sheets V. A comparison of methods to test mediation and other intervening variable effects. Psychol Methods. 2002;7(1):83-104.
57. Preacher K, Hayes A. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. Behav Res Methods 2008;40(3):879-91.
58. Babyak MA. What you see may not be what you get: A brief, nontechnical introduction to overfitting in regression-type models. Psychosom Med. 2004;66(3):411-21.
59. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol. 1996;49(12):1373-9.
60. Freedland KE, Babyak MA, McMahon RJ, Jennings JR, Golden RN, Sheps DS. Statistical guidelines for psychosomatic medicine. Psychosom Med. 2005;67(2):167.
61. Preacher K, Hayes A. SPSS and SAS procedures for estimating indirect effects in simple mediation models. Behav Res Methods. 2004;36(4):717-31.
62. Nykliček I, van Beugen S, Denollet J. Effects of mindfulness-based stress reduction on distressed (Type D) personality traits: A randomized controlled trial. J Behav Med. 2012;36(4):361-70.
63. Roncella A, Giornetti A, Cianfrocca C, Pasceri V, Pelliccia F, Denollet J, et al. Rationale and trial design of a randomized, controlled study on short-term psychotherapy after acute myocardial infarction: The STEP-IN-AMI trial (Short Term Psychotherapy in Acute Myocardial Infarction). J Cardiovasc Med. 2009;10(12):947-452
64. Haworth JE, Moniz-Cook E, Clark AL, Wang M, Cleland JGF. An evaluation of two self-report screening measures for mood in an out-patient chronic heart failure population. Int J Geriatr Psychiatry. 2007;22(11):1147-53.

CHAPTER 8

Psychological distress, inflammation, and IVUS plaque burden in patients treated with percutaneous coronary intervention

Damen NL, Versteeg H, Mommersteeg PMC, Cheng JM, Garcia-Garcia HM, de Jaegere PP, van Domburg RT, Pedersen SS, Boersma E. Submitted for publication.

ABSTRACT

Background: Psychological distress is associated with poor prognosis in patients with coronary artery disease (CAD). Both inflammation and the extent of coronary plaque burden are proposed as possible underlying mechanisms. We examined whether anxiety, depression, and the distressed (Type D) personality were associated with inflammatory markers and the extent of coronary plaque burden, as represented by intravascular ultrasound (IVUS), in patients treated with percutaneous coronary intervention (PCI).

Methods: The study sample of this cross-sectional study comprised 183 patients undergoing PCI. Blood samples for determining the inflammatory markers C-reactive protein (CRP), tumor-necrosis factor alpha (TNF-α), soluble TNF-α receptor 2 (sTNF-R2), interferon-gamma (IFN-γ), interleukin-8 (IL-8), interleukin-10 (IL-10), interleukin-18 (IL-18), and vascular cell adhesion molecule-1 (VCAM-1) were collected, and the extent of plaque burden was assessed by IVUS of a non-culprit coronary artery. Psychological distress was examined by the State measure of the State-Trait Anxiety Inventory (STAI-S), the Patient Health Questionnaire (PHQ-9), and the Type D scale (DS14).

Results: In multivariate analyses, consistent, but *inverse* associations were found between anxiety, Type D personality, negative affectivity (NA), and social inhibition (SI) and ln-transformed CRP level, whereas SI was associated with lower ln-transformed TNF-α levels. Both anxiety and NA were *inversely* associated with IVUS-derived coronary plaque burden. No significant associations were found for depression. Psychological distress accounted for 2-7% of the variance in inflammatory marker levels and coronary plaque burden.

Conclusion: Our results do not support inflammation and the extent of coronary plaque burden as likely mechanisms underlying the relationship between psychological distress and cardiovascular disease.

INTRODUCTION

Psychological distress, such as anxiety, depression, and the distressed (Type D) personality (i.e., the combination of negative affectivity and social inhibition traits [1]) is prevalent in 25-50% of patients with coronary artery disease (CAD) and associated with increased cardiovascular morbidity and mortality [1-4]. Both inflammation and the extent of atherosclerosis have been associated with the onset and progression of CAD [5-10]. These phenomena are also proposed as possible mechanisms linking psychological distress to poorer prognosis in CAD patients, although results are inconsistent.

Previous studies indicated that depressed or anxious CAD patients have higher levels of inflammatory markers, including C-reactive protein (CRP) [11-15] and interleukin-6 (IL-6) [11, 14], with these findings being confirmed in a meta-analysis [16]. In addition, Type D personality has been associated with higher levels of tumor-necrosis factor alpha (TNF-α), soluble TNF-α receptors 1 (sTNF-R1) and 2 (sTNF-R2), and lower levels of anti-inflammatory marker interleukin-10 (IL-10) in heart failure patients [17, 18]. However, other studies found no significant positive [19-22] or inverse associations [23] between psychological distress and inflammatory markers in CAD.

There is some evidence from population-based studies linking anxiety, depression, and personality traits to the presence, development, and progression of atherosclerosis [24-27], while negative findings are also reported [28-32]. In the latter studies, different standardized methods were used to assess the extent of atherosclerosis, including carotid intima-media-thickness (IMT) [25-27, 30-32], coronary artery calcification (CAC) [28, 29], and the Ankle-Brachial Index (ABI) [24, 26]. A relatively novel, intra-coronary imaging technique to obtain specific and detailed information on the extent of atherosclerosis and morphology is intravascular ultrasound (IVUS). By means of IVUS, specific and detailed information on the extent of coronary plaque burden can be obtained [33].

To our knowledge no study has reported on the association between psychological distress and IVUS-derived measures of coronary plaque burden. In addition, evidence on the association between psychological distress, inflammation, and the extent of atherosclerosis in CAD remains inconclusive. Hence, the aims of the current study were to examine whether anxiety, depression, and Type D personality were associated with 1) inflammatory markers (i.e., CRP, TNF-α, sTNF-R2, interferon-gamma (IFN-γ), interleukin-8 (IL-8), IL-10, interleukin-18 (IL-18), and vascular cell adhesion molecule-1 (VCAM-1)), and 2) IVUS plaque burden, in patients treated with percutaneous coronary intervention (PCI) with drug-eluting stenting.

METHODS

Participants and procedure

The current study was embedded in the European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis – Intravascular Ultrasound (ATHEROREMO-IVUS) study. The design of the ATHEROREMO-IVUS study has been published previously [33]. In brief, patients who underwent diagnostic coronary angiography or PCI for acute coronary syndrome (ACS) or stable angina pectoris were enrolled in ATHEROREMO-IVUS. Blood samples to assess inflammatory markers were drawn prior to the coronary catheterization or PCI procedure, whereas IVUS imaging of a non-culprit coronary artery to assess the extent of coronary plaque burden was performed subsequent to angiography or PCI.

Between November, 2008 and January, 2011, a total of 581 patients, of which 440 PCI patients, were enrolled in ATHEROREMO-IVUS in the Erasmus MC, Rotterdam, the Netherlands. During the study period, as part of an evaluation of our cardiac rehabilitation program, 256 patients who underwent PCI were asked to complete a set of standardized and validated psychological questionnaires within 4 weeks post-procedure (referred to as baseline in the remainder of the paper). Preliminary evidence suggests that psychological assessment at the time of the index-PCI may be less optimal than 1 month post-procedure [34]. Our study sample comprised the 183 responders (response rate 71%), who had complete data on blood samples, IVUS imaging, and psychological assessment.

The ATHEROREMO-IVUS study protocol was approved by the medical ethics committee of the Erasmus MC, Rotterdam, and the study was conducted according to the Helsinki Declaration [35]. Every patient provided written informed consent.

Measures

Socio-demographic and clinical characteristics

Socio-demographic characteristics included gender and age. Clinical characteristics included multi-vessel disease (multi-vessel disease vs. single-vessel disease/no vessel disease), body mass index (BMI), cardiac history (i.e., previous myocardial infarction (MI), coronary artery bypass graft (CABG) surgery, or PCI), indication for PCI (stable angina/silent ischemia, unstable angina, or MI), renal impairment, peripheral artery disease (PAD), chronic obstructive pulmonary disease (COPD), heart failure, CAD risk factors (i.e., hypertension, hypercholesterolemia, diabetes mellitus, family history of CAD, and self-reported smoking), and prescribed cardiac medications (i.e., ACE-inhibitors, aspirin, beta-blockers, calcium-antagonists, clopidogrel, diuretics, oral anti-coagulants, oral nitrates, and statins). Information on clinical variables was prospectively collected at the time of the index-PCI and recorded into a dedicated database.

Inflammatory markers

Blood samples to assess markers of inflammation were drawn from the arterial sheath prior to the PCI procedure. Within 2 hours after blood collection, blood samples were transported to the clinical laboratory of the Erasmus MC for further processing and storage at a temperature of -80°C. Inflammatory markers IFN-γ, IL-8, IL-10, IL-18, TNF-α, sTNF-R2, and VCAM-1 were measured in the stored EDTA-plasma samples using a validated multiplex assay (Custom Human Map, Myriad RBM, Austin, Texas, USA). TNF-α, IFN- γ, IL-8, IL-10, and IL-18 concentrations were reported in pg/ml, whereas sTNF-R2 and VCAM-1 concentrations were reported in ng/ml. The Roche Integra high-sensitivity assay was used to measure serum levels of CRP (mg/l) (Clinical laboratory, Erasmus MC, Rotterdam, the Netherlands).

IVUS plaque burden

Subsequent to the standard PCI procedure, IVUS imaging was used to assess the extent of atherosclerosis, as represented by the percentage of coronary plaque burden in a non-culprit coronary vessel (i.e., IVUS plaque burden). Selection of the non-culprit vessel was predefined in the study protocol. The order of preference for selection of the non-culprit vessel was: 1) left anterior descending (LAD) artery, 2) right coronary artery (RCA), and 3) left circumflex (LCX) artery. All IVUS data was acquired with the Volcano s5/s5i Imaging System (Volcano Corp., San Diego, CA, USA), using a Volcano Eagle Eye Gold IVUS catheter (20 MHz). An automatic pullback system was used with a standard pullback speed of 0.5 mm per second. The IVUS images were analyzed offline by an independent core laboratory (Cardialysis BV, Rotterdam, the Netherlands) that had no knowledge of the clinical data and inflammatory marker concentrations. The IVUS gray-scale was performed using pcVH 2.1 and qVH software (Volcano Corp., San Diego, CA, USA). The external elastic membrane and luminal borders were contoured for each frame (median interslice distance 0.4 mm). Extent and phenotype of the coronary plaque were assessed. Plaque burden was defined as the plaque and media cross-sectional area divided by the external elastic membrane cross-sectional area and is presented as a percentage.

Anxiety

Symptoms of anxiety were assessed at baseline with the Dutch version of the 20-item State measure of the State-Trait Anxiety Inventory (STAI-S) [36], a self-report instrument designed to measure the presence of axiety symptoms at the present moment. Each item is rated on a 4-point Likert scale ranging from 1 ("not at all") to 4 ("very much so"), with a score range of 20–80. A high score indicates high levels of anxiety, with a score ≥40 indicating probable clinical levels [37]. The STAI-S is a valid and reliable scale, with Cronbach's alpha ranging from .87 to .92 [36].

Depression

At baseline, patients completed the Dutch version of the 9-item Patient Health Questionnaire (PHQ-9), a self-report instrument that measures the frequency of depressive symptoms corresponding to the 9 diagnostic criteria for major depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM–IV) [38]. Patients were asked to indicate the frequency of experiencing the 9 depressive symptoms during the last 2 weeks on a 4-point Likert scale ranging from 0 ("not at all") to 3 ("nearly every day"), with a total score range of 0-27 [39]. The total score can be interpreted as indicating either no depression, minimal, mild, moderate, moderately severe, or severe depression. The PHQ-9 has demonstrated excellent validity when compared with a mental health interview for depression in patients with CAD [40, 41].

Type D personality

At baseline, Type D personality was assessed with the 14-item Type D scale (DS14) that comprises 2 subscales, negative affectivity (NA) (e.g., "I often feel unhappy") and social inhibition (SI) (e.g., "I am a closed kind of person"), each consisting of 7 items. Items are scored on a 5-point Likert scale ranging from 0 ("false") to 4 ("true"). Based on findings from the Item Response Theory [42], a standardized cut-off score ≥10 on both subscales is used to identify individuals with a Type D personality. Previous research suggests that the co-occurrence of NA and SI, rather than the single traits, predicts adverse events in PCI patients [43], and both continuous subscales were examined in the present study as well. The DS14 is internally consistent [44], not confounded by disease severity [45, 46], and relatively stable over time [45, 46].

Statistical analyses

Prior to analyses, all inflammatory markers (i.e., TNF-α, sTNF-R2, CRP, IFN-γ, IL-8, IL-10, IL-18, and VCAM-1) were ln-transformed, as they were not normally distributed, and verified that ln-transformation resulted in normal distributions. Pearson correlation coefficient was used to estimate the correlations of anxiety, depression, and the 2 continuous components of Type D personality (NA and SI), with the continuous ln-transformed inflammatory markers and IVUS plaque burden.

Second, univariable and multivariable linear regression analyses were conducted to examine whether anxiety, depression, Type D personality, NA, and SI were associated with the inflammatory markers and IVUS plaque burden. In these linear models, symptoms of anxiety and depression and the scores on the distinct NA and SI subscales were entered as continuous independent variables, Type D personality as a dichotomous independent variable, and the continuous ln-transformed inflammatory marker concentrations and IVUS plaque burden as the dependent variables. In multivariable linear regression

analyses, we adjusted for socio-demographic characteristics (i.e., gender and age), clinical characteristics (i.e., multi-vessel disease, BMI, cardiac history, indication for PCI, CAD risk factors (i.e., hypertension, hypercholesterolemia, diabetes mellitus, family history of CAD, and self-reported smoking), and prescribed cardiac discharge medications (i.e., ACE-inhibitors, beta-blockers, calcium-antagonists, diuretics, oral nitrates, and statins)). Covariates were entered into the model using the Enter method, thereby reducing the risk of overfitting [47], and selected a priori based on the literature [11, 13, 14, 23, 48, 49].

Separate linear models were conducted for the different inflammatory markers, IVUS plaque burden, and the different psychological factors (i.e., anxiety, depression, Type D personality, NA, and SI). All results were based on 2-tailed tests and a *p*-value <.05 was used to indicate statistical significance. All statistical analyses were performed using SPSS for Windows 19.0 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Patient characteristics

The study sample comprised 183 patients treated with PCI, who had complete data on blood samples, IVUS imaging, and psychological assessment (73.8% men; mean age 63.7±10.9 years, range [32-88] years). The mean anxiety score at baseline was 34.9±11.6, whereas the mean baseline depression score was 4.7±4.5. At baseline, the prevalence of Type D personality was 25.1% (45/183), whereas mean baseline scores for NA and SI were 8.3±6.0 and 8.0±6.0, respectively. Detailed patient characteristics are presented in Table 1.

Table 1. Patient characteristics for the total sample

	Total sample (N=183)
Socio-demographic characteristics	
Male gender	135 (73.8)
Age, mean (SD)	63.7 (10.9)
Clinical characteristics	
Multi-vessel disease	77 (44.0)
Cardiac history [b]	83 (45.4)
Indication for PCI	
Stable angina/ Silent ischemia	90 (49.2)
Unstable angina	51 (27.9)
MI	41 (22.4)
Hypertension	90 (49.2)
Hypercholesterolemia	98 (53.6)
Diabetes mellitus	29 (15.8)
Family history of CAD	98 (53.6)
Self-reported smoking	47 (25.7)
BMI, mean (SD)	27.4 (4.0)
Renal impairment	9 (4.9)
Peripheral artery disease	14 (7.7)
Chronic obstructive pulmonary disease	11 (6.0)
Heart failure	5 (2.7)
Cardiac medication	
Aspirin	180 (98.4)
ACE-inhibitors	108 (59.7)
Beta-blockers	131 (72.8)
Calcium-antagonists	43 (23.8)
Clopidogrel	175 (97.2)
Diuretics	28 (15.5)

Table 1. *Continued*

	Total sample (N=183)
Oral anti-coagulants	9 (5.0)
Oral nitrates	38 (21.1)
Statins	162 (90.0)
Inflammatory markers	
CRP (mg/l), median (IQR)	1.9 (.7 - 4.5)
IFN-γ (pg/ml), median (IQR)	5.4 (3.9 - 7.7)
IL-8 (pg/ml), median (IQR)	9.2 (6.7 - 12.0)
IL-10 (pg/ml), median (IQR)	5.2 (3.1 - 10.0)
IL-18 (pg/ml), median (IQR)	162.5 (125.3 - 208.8)
TNF-α (pg/ml), median (IQR)	1.9 (1.0 - 3.0)
TNF-R2 (ng/ml), median (IQR)	4.6 (3.6 - 5.8)
VCAM-1 (ng/ml), median (IQR)	433.0 (351.0 - 513.0)
The extent of coronary plaque burden	
IVUS plaque burden (%), mean (SD)	38.0 (11.6)
Psychological factors	
Anxiety, mean (SD)	34.9 (11.6)
Depression, mean (SD)	4.7 (4.5)
Type D personality	45 (25.1)
Negative affectivity, mean (SD)	8.3 (6.0)
Social inhibition, mean (SD)	8.0 (6.0)

[a] Results are presented as n (%) unless otherwise stated

[b] Previous myocardial infarction (MI), percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG) surgery

ACE = angiotensin-converting enzyme, BMI = Body mass index (kg/m^2), CAD = coronary artery disease, CRP = C-reactive protein, IFN-γ = interferon-gamma, IL-8 = interleukin-8, IL-10 = interleukin-10, IL-18 = interleukin-18, IQR = inter quartile range, IVUS = intravascular ultrasound, sTNF-R2 = soluble TNF-α receptor 2, TNF-α = tumor-necrosis factor alpha, VCAM-1 = vascular cell adhesion molecule-1

Associations between psychological distress, inflammatory markers, and IVUS plaque burden

Anxiety was inversely correlated with ln CRP levels (*r*=-.22) and IVUS plaque burden (*r*=-.17). With regard to the 2 components of Type D personality, both NA and SI were inversely correlated with ln CRP (*r*=-.19 and *r*=-.21, respectively). Further, NA was inversely correlated with ln IL-8 (*r*=-.16) and IVUS plaque burden (*r*=-.18), whereas SI was inversely correlated with ln TNF-α (*r*=-.16) and ln IL-10 (*r*=-.19). No significant correlations were found between depression, the inflammatory markers, and IVUS plaque burden (Table 2).

Univariable linear regression analyses showed that anxiety was inversely associated with level of ln CRP (B=-.03, *p*=.004, R^2=.05) and IVUS plaque burden (B=-.18, *p*=.025, R^2=.03). In multivariable analyses, these associations remained significant after adjusting for socio-demographic and clinical characteristics. Type D personality was inversely associated with ln CRP (B=-.65, *p*=.009, R^2=.04) and ln IL-10 (B=-.45, *p*=.014, R^2=.04) in univariable analyses. In multivariable analyses, the association between Type D personality and ln CRP remained significant, but the inverse association with ln IL-10 was no longer significant (Table 3).

With regard to the 2 components of Type D personality, NA was inversely associated with ln CRP (B=-.05, *p*=.011, R^2=.04), ln IL-8 (B=-.01, *p*=.034, R^2=.03), and IVUS plaque burden (B=-.34, *p*=.019, R^2=.03) in univariable analyses. Multivariable analyses yielded the same results, except for the association between NA and IL-8, which was no longer significant after adjusting for socio-demographic and clinical characteristics. In addition, in multivariable analyses NA was significantly associated with higher ln VCAM-1 levels. For SI, in univariable analyses significant inverse associations were found with ln CRP (B=-.05, *p*=.004, R^2=.05), ln TNF-α (B=-.02, *p*=.028, R^2=.03), and ln IL-10 (B=-.03, *p*=.021, R^2=.04), which remained significant in multivariable analyses. No significant associations were found between depression and the inflammatory markers or IVUS plaque burden. In general, in multivariable analyses psychological distress accounted for 2-7% of the variance in inflammatory marker and IVUS plaque burden levels (Table 3).

Table 2. Correlations between psychological distress, inflammatory markers, and IVUS plaque burden

	Anxiety	***Depression***	***Type D personality***	
			NA	***SI***
Inflammatory markers				
Ln CRP	-.22**	-.10	-.19*	-.21**
Ln TNF-α	-.04	-.06	-.07	-.16*
Ln TNF-R2	.11	-.01	.07	.04
Ln IFN-γ	-.04	.09	-.02	.03
Ln IL-8	-.05	.03	-.16*	.04
Ln IL-10	.02	-.08	-.12	-.19*
Ln IL-18	-.01	-.05	-.05	-.12
Ln VCAM-1	.15	.13	.13	.12
The extent of coronary plaque burden				
IVUS plaque burden	-.17*	-.10	-.18*	-.02
Psychological factors				
Anxiety	-	.57**	.70**	.38**
Depression	-	-	.56**	.33**
Negative affectivity (NA)	-	-	-	.45**
Social inhibition (SI)	-	-	-	1

*$p \leq .05$; ** $p \leq .01$; ***$p \leq .001$

CRP = C-reactive protein, IFN-γ = interferon-gamma, IL-8 = interleukin-8, IL-10 = interleukin-10, IL-18 = interleukin-18, IVUS = intravascular ultrasound, sTNF-R2 = soluble TNF-α receptor 2, TNF-α = tumor-necrosis factor alpha, VCAM-1 = vascular cell adhesion molecule-1

Table 3. Linear regression analyses on the association between psychological distress, inflammatory markers, and IVUS plaque burden (adjusted analyses[a])

	Ln CRP				***Ln TNF-α***				***Ln TNF-R2***			
	B	***SE B***	***ΔR²***	***R²***	***B***	***SE B***	***ΔR²***	***R²***	***B***	***SE B***	***ΔR²***	***R²***
Anxiety	-.04***	.01	.07	.22	-.003	.01	.002	.09	.003	.003	.01	.23
Depression	-.03	.03	.01	.14	.02	.01	.02	.10	.01	.01	.02	.23
Type D personality	-.63*	.27	.03	.16	-.27	.14	.02	.09	-.001	.07	.000	.20
Negative affectivity (NA)	-.04*	.02	.03	.16	-.01	.01	.003	.07	.01	.01	.01	.21
Social inhibition (SI)	-.05**	.02	.04	.17	-.02*	.01	.03	.10	.001	.01	.000	.21

Table 3. *Continued*

	Ln IFN-γ				Ln IL-8				Ln IL-10			
	B	***SE B***	**ΔR^2**	**R^2**	***B***	***SE B***	**ΔR^2**	**R^2**	***B***	***SE B***	**ΔR^2**	**R^2**
Anxiety	.000	.004	.000	.23	-.003	.003	.004	.20	.003	.01	.001	.28
Depression	.01	.01	.003	.21	-.01	.01	.01	.22	.01	.02	.001	.29
Type D personality	-.01	.11	.000	.20	-.04	.08	.001	.22	-.34	.19	.02	.31
Negative affectivity (NA)	.001	.01	.000	.20	-.01	.01	.01	.23	-.01	.01	.004	.29
Social inhibition (SI)	.000	.01	.000	.20	-.01	.01	.01	.22	-.03*	.01	.03	.32

Table 3. *Continued*

	Ln IL-18				*Ln VCAM-1*				*IVUS plaque burden*			
	B	***SE B***	**ΔR^2**	**R^2**	***B***	***SE B***	**ΔR^2**	**R^2**	***B***	***SE B***	**ΔR^2**	**R^2**
Anxiety	.001	.004	.001	.11	.004	.002	.02	.30	-.17*	.09	.03	.16
Depression	.01	.01	.01	.13	.01	.01	.01	.28	-.34	.21	.02	.17
Type D personality	-.05	.09	.002	.12	.02	.05	.001	.28	-3.76	2.18	.02	.16
Negative affectivity (NA)	-.003	.01	.002	.12	.01*	.003	.02	.31	-.36*	.15	.03	.17
Social inhibition (SI)	-.01	.01	.03	.15	.003	.003	.003	.29	-.10	.16	.002	.14

*$p \leq .05$; ** $p \leq .01$; ***$p \leq .001$

[a] after adjusting for gender, age, multi-vessel disease, body mass index (BMI), cardiac history (i.e., previous myocardial infarction (MI), percutaneous coronary intervention (PCI), or coronary artery bypass graft surgery (CABG)), indication for PCI (i.e., stable angina/silent ischemia, unstable angina, or MI), hypertension, hypercholesterolemia, diabetes mellitus, family history of coronary artery disease (CAD), self-reported smoking, and prescribed ACE-inhibitors, beta-blockers, calcium-antagonists, diuretics, oral nitrates, and statins

B: per unit increase in ln-transformed biomarker concentration

ΔR^2 compared to the model including all other variables, R^2 for the full model

CRP = C-reactive protein, IFN-γ = interferon-gamma, IL-8 = interleukin-8, IL-10 = interleukin-10, IL-18 = interleukin-18, IVUS = intravascular ultrasound, sTNF-R2 = soluble TNF-α receptor 2, TNF-α = tumor-necrosis factor alpha, VCAM-1 = vascular cell adhesion molecule-1

DISCUSSION

We found consistent, although small, inverse associations between psychological distress and serum levels of CRP and TNF-α. Anxiety and NA were inversely associated with IVUS-derived coronary plaque burden. We consider these findings counterintuitive, as increased levels of distress were related to lower levels of inflammatory markers or IVUS plaque burden. No associations were found between depression and inflammatory markers or coronary plaque burden. Overall, these results do not support inflammation and the extent of coronary plaque burden as likely mechanisms underlying the relationship between psychological distress and cardiovascular disease in PCI patients.

We could not confirm the findings of previous studies in CAD patients showing that anxiety, depression, and Type D personality were associated with higher levels of inflammatory markers [11-18]. Previous studies have mainly focused on CRP [11-16], IL-6 [11, 14, 16], and TNF-α and its soluble receptors [17, 18], whereas we studied a wide variety of inflammatory markers, but not IL-6. In the present study, all participants were eligible for PCI, whereas previous studies mainly enrolled patients with stable CAD [11, 13], ACS [12], or heart failure [17, 18]. These different clinical phenotypes may be associated with various inflammatory marker expressions reflecting their intrinsic pathophysiological processes.

In the present study, anxiety, Type D personality, NA, and SI were *inversely* related with the inflammatory markers CRP and TNF-α, showing that elevated distress was related to *lower* levels of these inflammatory markers. Psychological distress was associated with lower levels of inflammation in one previous study, demonstrating inverse associations between depression and CRP, fibrinogen, and IL-6 in patients with established CAD [23]. Psychological distress is known to be associated with increased levels of cortisol, whereas hypercortisolemia is known to have anti-inflammatory effects. Increased cortisol levels (which we did not measure) in distressed patients might have contributed to lower levels of inflammation [23]. It might be worthwhile to evaluate this hypothesis in future studies, although we realize that the observed inverse effects were small and in disagreement with several other investigations.

Besides these small inverse associations, in the current study no further significant associations were found between anxiety, depression, Type D personality, and the inflammatory markers. A lack of association between psychological distress and inflammation [19-22] has been reported previously. Inflammatory variables in the present study reflect a state of significant obstructive coronary occlusion, as blood samples were collected immediately before the PCI procedure. Distress scores were examined within 4 weeks after the procedure, to prevent an effect of the procedure on mood states [34]. A ceiling effect, in which the presence of psychological distress cannot further increase the already elevated levels of inflammatory markers in CAD patients, has been suggested [19, 23].

However, this explanation seems hardly likely in the present study, given that average CRP levels were not extremely elevated (31.7% >3 mg/l) [50, 51].

In our study, higher levels of anxiety and NA were associated with *lower* coronary plaque burden, as measured by IVUS, whereas depression was not related to coronary plaque burden. The associations were small, explaining 2-3% of the variance in IVUS detected. IVUS-derived coronary plaque burden has not been related to distress before, but other studies have examined other measures of coronary plaque burden, such as IMT [25-27, 30-32], CAC [28, 29], or ABI [24, 26]. The present findings contrast previous studies, in which anxiety, depression, and personality traits were significantly associated with an *increased* coronary plaque burden [24-27]. At the same time, other studies did not find an association between psychological distress and the extent of coronary plaque burden [28-32].

The results of the current study do not support increased inflammation and the extent of coronary plaque burden as measured by IVUS as likely mechanisms underlying the relationship between psychological distress and CAD in patients with PCI. Possibly, other biological or behavioral mechanisms could provide a more robust explanation for this link, as was suggested in previous studies. For example, psychologically distressed patients may be less likely to engage in optimal health-related behaviors, such as exercising, quitting smoking, and adhering to dietary constrictions [11, 52-54]. In addition, psychological distress may alter the activity of the autonomic nervous system, leading to increases in blood pressure and reduced heart rate variability [52, 55-57]. Future studies should further investigate the potential pathways through which psychological distress may have an adverse influence on prognosis in patients with CAD.

Strengths of the current study include the wide variety of inflammatory markers assessed and the focus on the association between psychological distress and IVUS-derived measures of coronary plaque burden. However, some limitations of the current study should be acknowledged. First, the cross-sectional study design does not allow for causal inferences about the relationship between anxiety, depression, Type D personality, inflammation, and IVUS plaque burden. Until now it remains unclear whether psychological distress may lead to increased inflammation and coronary plaque burden or whether it is the other way around. Future studies using a longitudinal design are warranted to examine the directionality of the relationship between anxiety, depression, Type D personality, inflammation, and IVUS plaque burden. Second, we did not have information on the commonly investigated inflammatory marker IL-6. Third, because inflammatory and atherosclerotic processes are influenced by many factors, the current study may be underpowered to detect the effects of psychological distress on these processes due to a limited sample size.

In conclusion, the results of the current study do not support increased inflammation and the extent of coronary plaque burden as likely mechanisms underlying the relationship between psychological distress and CAD, as inverse associations were found between anxiety, Type D personality, inflammation, and IVUS plaque burden in patients treated with PCI, whereas for depression no significant associations were found. Large-scale prospective studies are warranted to further disentangle the underlying mechanisms between psychological distress and cardiovascular disease.

ACKNOWLEDGEMENTS

The ATHEROREMO-IVUS study is embedded in The European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis (ATHEROREMO) and is funded by the Seventh Framework Program (FP7), theme FP7-HEALTH-2007-2.4.2-1. This research was in part supported with a VIDI grant (91710393) from the Netherlands Organization for Health Research and Development (ZonMW), The Hague, the Netherlands, to Dr. S.S. Pedersen.

REFERENCES

1. Denollet J, Pedersen SS, Vrints CJ, Conraads VM. Usefulness of Type D personality in predicting five-year cardiac events above and beyond concurrent symptoms of stress in patients with coronary heart disease. Am J Cardiol. 2006;97(7):970-3.
2. Meijer A, Conradi HJ, Bos EH, Thombs BD, van Melle JP, de Jonge P. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: A meta-analysis of 25 years of research. Gen Hosp Psychiatry. 2011;33(3):203-16.
3. Roest AM, Martens EJ, Denollet J, de Jonge P. Prognostic association of anxiety post myocardial infarction with mortality and new cardiac events: A meta-analysis. Psychosom Med. 2010;72(6):563-9.
4. Connerney I, Sloan RP, Shapiro PA, Bagiella E, Seckman C. Depression is associated with increased mortality 10 years after coronary artery bypass surgery. Psychosom Med. 2010;72(9):874-81.
5. Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. N Engl J Med. 2004;350(14):1387-97.
6. Ridker PM, Rifai N, Pfeffer M, Sacks F, Lepage S, Braunwald E. Elevation of tumor necrosis factor-α and increased risk of recurrent coronary events after myocardial infarction. Circulation. 2000;101(18):2149-53.
7. Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. Circulation. 2000;101(15):1767-72.
8. Willerson JT, Ridker PM. Inflammation as a cardiovascular risk factor. Circulation. 2004;109(21 suppl 1):II2-10.
9. Johnsen SH, Mathiesen EB, Joakimsen O, Stensland E, Wilsgaard T, Løchen M, et al. Carotid atherosclerosis is a stronger predictor of myocardial infarction in women than in men: A 6-year follow-up study of 6226 persons: The Tromsø Study. Stroke. 2007;38(11):2873-80.
10. van der Meer IM, Bots ML, Hofman A, Iglesias del Sol A, van der Kuip DAM, Witteman JCM. Predictive value of noninvasive measures of atherosclerosis for incident myocardial infarction: The Rotterdam Study. Circulation. 2004;109(9):1089-94.
11. Duivis HE, de Jonge P, Penninx BW, Ya Na B, Cohen BE, Whooley MA. Depressive symptoms, health behaviors, and subsequent inflammation in patients with coronary heart disease: Prospective findings from the Heart and Soul Study. Am J Psychiatry. 2011;168(9):913-20.
12. Miller GE, Freedland KE, Duntley S, Carney RM. Relation of depressive symptoms to C-reactive protein and pathogen burden (cytomegalovirus, herpes simplex virus, Epstein-Barr virus) in patients with earlier acute coronary syndromes. Am J Cardiol. 2005;95(3):317-21.
13. Bankier B, Barajas J, Martinez-Rumayor A, Januzzi JL. Association between C-reactive protein and generalized anxiety disorder in stable coronary heart disease patients. Eur Heart J. 2008;29(18):2212-7.
14. Vaccarino V, Johnson BD, Sheps DS, Reis SE, Kelsey SF, Bittner V, et al. Depression, inflammation, and incident cardiovascular disease in women with suspected coronary ischemia: The National Heart, Lung, and Blood Institute sponsored WISE Study. J Am Coll Cardiol. 2007;50(21):2044-50.
15. Gegenava T, Gegenava M, Kavtaradze G. C-reactive protein level correlation with depression and anxiety among patients with coronary artery disease. Georgian Med News. 2011;194:34-7.
16. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: A meta-analysis. Psychosom Med. 2009;71(2):171-86.
17. Denollet J, Schiffer AA, Kwaijtaal M, Hooijkaas H, Hendriks EH, Widdershoven JW, et al. Usefulness of Type D personality and kidney dysfunction as predictors of interpatient variability in inflammatory activation in chronic heart failure. Am J Cardiol. 2009;103(3):399-404.

18. Conraads VM, Denollet J, de Clerck LS, Stevens WJ, Bridts C, Vrints CJ. Type D personality is associated with increased levels of tumour necrosis factor (TNF)-α and TNF-α receptors in chronic heart failure. Int J Cardiol. 2006;113(1):34-8.
19. Schins A, Tulner D, Lousberg R, Kenis G, Delanghe J, Crijns H, et al. Inflammatory markers in depressed post-myocardial infarction patients. J Psychiatr Res. 2005;39(2):137-44.
20. Steptoe A, Wikman A, Molloy GJ, Messerli-Bürgy N, Kaski J. Inflammation and symptoms of depression and anxiety in patients with acute coronary heart disease. Brain Behav Immun. 2012;31:183-8.
21. Smolderen KG, Spertus JA, Reid KJ, Buchanan DM, Vaccarino V, Lichtman JH, et al. Association of somatic and cognitive depressive symptoms and biomarkers in acute myocardial infarction: Insights from the translational research investigating underlying disparities in acute myocardial infarction patients' health status registry. Biol Psychiatry. 2012;71(1):22-9.
22. Janszky I, Lekander M, Blom M, Georgiades A, Ahnve S. Self-rated health and vital exhaustion, but not depression, is related to inflammation in women with coronary heart disease. Brain Behav Immun. 2005;19(6):555-63.
23. Whooley MA, Caska CM, Hendrickson BE, Rourke MA, Ho J, Ali S. Depression and inflammation in patients with coronary heart disease: Findings from the Heart and Soul Study. Biol Psychiatry. 2007;62(4):314-20.
24. Seldenrijk A, Vogelzangs N, van Hout HPJ, van Marwijk HWJ, Diamant M, Penninx BWJH. Depressive and anxiety disorders and risk of subclinical atherosclerosis: Findings from the Netherlands Study of Depression and Anxiety (NESDA). J Psychosom Res. 2010;69(2):203-10.
25. Rosenström T, Jokela M, Cloninger CR, Hintsanen M, Juonala M, Raitakari O, et al. Associations between dimensional personality measures and preclinical atherosclerosis: The cardiovascular risk in Young Finns study. J Psychosom Res. 2012;72(5):336-43.
26. Tiemeier H, van Dijck W, Hofman A, Witteman JM, Stijnen T, Breteler MB. Relationship between atherosclerosis and late-life depression: The Rotterdam study. Arch Gen Psychiatry. 2004;61(4):369-76.
27. Paterniti S, Zureik M, Ducimetière P, Touboul P, Fève J, Alpérovitch A. Sustained anxiety and 4-year progression of carotid atherosclerosis. Arterioscler Thromb Vasc Biol. 2001;21(1):136-41.
28. Devantier TA, Nørgaard BL, Sand NP, Mols RE, Foldager L, Diederichsen ACP, et al. Lack of correlation between depression and coronary artery calcification in a non-selected Danish population. Psychosomatics. 2013;54(5):458-65.
29. O'Malley PG, Jones DL, Feuerstein IM, Taylor AJ. Lack of correlation between psychological factors and subclinical coronary artery disease. N Engl J Med. 2000;343(18):1298-304.
30. Seldenrijk A, van Hout HPJ, van Marwijk HWJ, de Groot E, Gort J, Rustemeijer C, et al. Carotid atherosclerosis in depression and anxiety: Associations for age of depression onset. World J Biol Psychiatry. 2011;12(7):549-58.
31. Beutel ME, Wiltink J, Kirschner Y, Sinning C, Espinola-Klein C, Wild PS, et al. History of depression but not current depression is associated with signs of atherosclerosis: Data from the Gutenberg Health Study. Psychol Med. 2013; In press, doi: 10.1017/S0033291713001542:1-7.
32. Ohira T, Diez Roux AV, Polak JF, Homma S, Iso H, Wasserman BA. Associations of anger, anxiety, and depressive symptoms with carotid arterial wall thickness: The multi-ethnic study of atherosclerosis. Psychosom Med. 2012;74(5):517-25.
33. de Boer SPM, Cheng JM, Garcia-Garcia HM, Oemrawsingh RM, van Geuns RJ, Regar E. Relation of genetic profile and novel circulating biomarkers with coronary plaque phenotype as determined by intravascular ultrasound: Rationale and design of the ATHEROREMO-IVUS study. EuroIntervention. 2013; In press; pii: 20130113-01.
34. Poston WSC, Haddock CK, Conard MW, Jones P, Spertus J. Assessing depression in the cardiac patient. Behav Modif. 2003;27(1):26-36.
35. Goodyear MDE, Krleza-Jeric K, Lemmens T. The declaration of Helsinki. Br Med J. 2007;335(7621):624-5.

36. van der Ploeg HMDP, Spielberger CD. Handleiding bij de Zelf-Beoordelings Vragenlijst (ZBV). Een Nederlandstalige bewerking van de Spielberger State-Trait Anxiety Inventory. Lisse: Swets & Zeitlinger BV; 1980.
37. Kvaal K, Ulstein I, Nordhus IH, Engedal K. The Spielberger State-Trait Anxiety Inventory (STAI): The state scale in detecting mental disorders in geriatric patients. Int J Geriatr Psychiatry. 2005;20(7):629-34.
38. Spitzer Rl, Kroenke K, Williams JW. Validation and utility of a self-report version of PRIME-MD: The PHQ primary care study. J Am Med Assoc. 1999;282(18):1737-44.
39. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9. J Gen Int Med. 2001;16(9):606-13.
40. Stafford L, Berk M, Jackson HJ. Validity of the Hospital Anxiety and Depression Scale and Patient Health Questionnaire-9 to screen for depression in patients with coronary artery disease. Gen Hosp Psychiatry. 2007;29(5):417-24.
41. Thombs BD, Ziegelstein RC, Whooley MA. Optimizing detection of major depression among patients with coronary artery disease using the Patient Health Questionnaire: Data from the Heart and Soul Study. J Gen Int Med. 2008;23(12):2014-7.
42. Emons WHM, Meijer RR, Denollet J. Negative affectivity and social inhibition in cardiovascular disease: Evaluating Type-D personality and its assessment using item response theory. J Psychosom Res. 2007;63(1):27-39.
43. Denollet J, Pedersen SS, Ong AT, Erdman RA, Serruys PW, van Domburg RT. Social inhibition modulates the effect of negative emotions on cardiac prognosis following percutaneous coronary intervention in the drug-eluting stent era. Eur Heart J. 2006;27(2):171-7.
44. Denollet J. DS14: Standard assessment of negative affectivity, social inhibition, and Type D personality. Psychosom Med. 2005;67(1):89-97.
45. de Jonge P, Denollet J, van Melle JP, Kuyper A, Honig A, Schene AH, et al. Associations of Type D personality and depression with somatic health in myocardial infarction patients. J Psychosom Res. 2007;63(5):477-82.
46. Martens EJ, Kupper N, Pedersen SS, Aquarius A, Denollet J. Type-D personality is a stable taxonomy in post-MI patients over an 18-month period. J Psychosom Res. 2007;63(5):545-50.
47. Babyak MA. What you see may not be what you get: A brief, nontechnical introduction to overfitting in regression-type models. Psychosom Med. 2004;66(3):411-21.
48. Freedland KE, Babyak MA, McMahon RJ, Jennings JR, Golden RN, Sheps DS. Statistical guidelines for psychosomatic medicine. Psychosom Med. 2005;67(2):167.
49. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol. 1996;49(12):1373-9.
50. Yun K, Jeong M, Oh S, Rhee S, Park E, Lee E, et al. Response of high-sensitivity C-reactive protein to percutaneous coronary intervention in patients with acute coronary syndrome. Heart Vessels. 2009;24(3):175-80.
51. Koc M, Karaarslan O, Abali G, Batur MK. Variation in high-sensitivity C-reactive protein levels over 24 hours in patients with stable coronary artery disease. Tex Heart Inst J. 2010;37(1):42-8.
52. Carney RM, Freedland KE, Miller GE, Jaffe AS. Depression as a risk factor for cardiac mortality and morbidity: A review of potential mechanisms. J Psychosom Res. 2002;53(4):897-902.
53. Gilmour J, Williams L. Type D personality is associated with maladaptive health-related behaviours. J Health Psychol. 2012;17(4):471-8.
54. Dempe C, Jünger J, Hoppe S, Katzenberger M, Möltner A, Ladwig KH, et al. Association of anxious and depressive symptoms with medication nonadherence in patients with stable coronary artery disease. J Psychosom Res. 2013;74(2):122-7.
55. von Känel R, Barth J, Kohls S, Saner H, Znoj H, Saner G, et al. Heart rate recovery after exercise in chronic heart failure: Role of vital exhaustion and type D personality. J Cardiol. 2009;53(2):248-56.
56. Watkins LL, Blumenthal JA, Carney RM. Association of anxiety with reduced baroreflex cardiac control in patients after acute myocardial infarction. Am Heart J. 2002;143(3):460-6.
57. Martens EJ, Nyklíček I, Szabó BM, Kupper N. Depression and anxiety as predictors of heart rate variability after myocardial infarction. Psychol Med. 2008;38(3):375-83.

CHAPTER 9

Cardiac patients who completed a longitudinal psychosocial study had a different clinical and psychosocial baseline profile than patients who dropped out prematurely

Damen NL, Versteeg H, Serruys PW, van Geuns RM, van Domburg RT, Pedersen SS, Boersma E. Eur J Prev Cardiol. 2013; In press, doi: 10.1177/2047487313506548.
Short report

ABSTRACT

Non-response is a serious threat to the external validity of longitudinal psychosocial studies. Little is known about potential systematic differences between patients with coronary artery disease who complete a psychosocial study and those who drop out prematurely due to non-response, and whether drop-outs may have a different cardiovascular risk. We studied a cohort of 1132 consecutive patients undergoing percutaneous coronary intervention (PCI). At baseline, all patients completed the Hospital Anxiety and Depression Scale (HADS) and the Type D Scale (DS14). At 12 months follow-up, 70.8% (n=802) of patients completed both questionnaires, while 29.2% (n=330) dropped out. We observed significant differences in socio-demographic, clinical, and psychological baseline characteristics between completers and drop-outs. Drop-outs were younger, more likely to smoke, but less often prescribed cardiovascular medications, including calcium-antagonists and ACE-inhibitors, as compared with completers. Drop-outs more often had depression, anxiety, and negative affectivity as compared with completers (all *p*-values <.05). After a median follow-up of 4 years, we found no significant differences in mortality risk between completers and drop-outs (6.5% versus 7.3%; adjusted HR=1.34; 95%CI [.82-2.19], *p*=.24, respectively). In conclusion, a possible attrition bias occurred, as drop-outs and completers differed systematically on some socio-demographic, clinical, and psychological baseline characteristics. Despite these differences, this did not translate into a poorer short-term prognosis, as there were no differences in the mortality risk of completers versus drop-outs after a median follow-up of 4 years. In future prospective studies, attention should be paid to attrition bias, and its possible impact on study results and implications should be discussed.

INTRODUCTION

The prospective cohort design in combination with standardized and validated questionnaires has been the primary methodology used to examine a link between psychological factors (e.g., anxiety, depression, and the distressed (Type D) personality (i.e., the combination of negative affectivity and social inhibition traits [1])) and prognosis in coronary artery disease (CAD) [1-6]. A potential attrition bias can be introduced when participants completing the study ("completers") and participants who are lost to follow-up ("drop-outs") differ systematically on baseline characteristics, exposure to risk factors, or outcome variables [7]. This is particularly a concern if there is a systematic loss to follow-up related to the potential risk factor under study, jeopardizing any conclusions drawn - being an over- or underestimation of the true effect - and the generalizability [8]. Previous studies have mainly focused on differences between participants and non-participants, finding a "healthy volunteer effect" with participants having a better general health as compared with non-participants [9-11], and an increased mortality risk in non-participants [7, 10, 12-14].

One previous study in post-myocardial infarction (MI) patients and one population-based study focused on systematic differences in outcome between completers and drop-outs, demonstrating that drop-out during follow-up was associated with a higher mortality risk [15, 16]. However, most studies do not report drop-out rates, reasons for drop-out, or compare the characteristics of drop-outs versus completers [17]. Hence, we know little about differences in baseline characteristics or exposure to risk factors between completers and drop-outs, and consequences to clinical outcome.

To our knowledge, no study has focused on potential systematic differences between completers and drop-outs when examining the prevalence of psychological factors and their impact on clinical outcome in CAD patients. Hence, the aims of the current study were to examine differences in 1) socio-demographic, clinical, and psychological (i.e., anxiety, depression, and Type D personality) baseline characteristics, and 2) 4-year risk for mortality between completers and drop-outs at 12 months in patients treated with percutaneous coronary intervention (PCI).

METHODS

Our sample comprised 1132 consecutive patients treated with PCI between July 1, 2003 and September 14, 2006 at the Erasmus MC, Rotterdam, the Netherlands. At baseline (i.e., 4 weeks post-PCI) and 12 months post-PCI, patients were asked to complete the Dutch version of the Hospital Anxiety and Depression Scale (HADS) to assess symptoms of anxiety and depression [18] and the Type D scale (DS14) to assess Type D personality [19].

Completers were defined as patients who completed the HADS and the DS14 both at baseline and at 12 months post-PCI, whereas drop-outs were defined as patients who completed the questionnaires at baseline, but not at 12 months post-PCI. Patients who dropped out of the study due to death between baseline and 12 months post-PCI were excluded from the analyses.

Differences in socio-demographic, clinical and psychological baseline characteristics between completers and drop-outs were examined using the Chi-square test for nominal variables and Student's t-test for independent samples for continuous variables. Differences in all-cause mortality between completers and drop-outs were examined using the Kaplan-Meier method and univariable and multivariable Cox regression models. In multivariable analysis, we adjusted for socio-demographic (i.e., gender and age), clinical (i.e., cardiac history, hypertension, diabetes mellitus, family history of CAD, and prescribed cardiac discharge medications (i.e., beta-blockers, calcium-antagonists, and statins)), and psychological (i.e., anxiety, depression, and Type D personality) baseline characteristics. Covariates were selected a priori based on the literature [13-16].

RESULTS

In the current study, at 12 months follow-up 70.8% (n=802) of patients were classified as completers and 29.2% (n=330) as drop-outs. Completers and drop-outs differed on several baseline characteristics, with drop-outs being younger (61.2 years vs. 63.2 years), more likely to smoke (27.5% vs. 17.4%), but less likely to be prescribed calcium-antagonists (18.9% vs. 34.1%) and ACE-inhibitors (28.4% vs. 39.6%) as compared with completers. Drop-outs were more likely to be depressed (28.5% vs. 20.5%), anxious (30.0% vs. 23.2%), and to report negative affectivity (mean score 9.3 vs. mean score 8.1) at baseline as compared with completers (Table 1). At a median follow-up of 4.3±1.2 years, the incidence of all-cause mortality was 6.5% (52/802) in completers versus 7.3% (24/330) in drop-outs. Cumulative hazard functions were not significantly different for completers versus drop-outs (log-rank X^2=.435, p=.51). In univariable and multivariable Cox regression analyses, there were no significant differences in all-cause mortality risk between completers and drop-outs (crude HR=1.18; 95%CI [.74-1.89], p=.48 and adjusted HR=1.34; 95%CI [.82-2.19], p=.24, respectively).

Table 1. Patient characteristics for the total sample and stratified by completers versus drop-outs [a]

	Total sample (N=1132)	***Completers (n=802)***	***Drop-outs [b] (n=330)***	***p***
Socio-demographic characteristics				
Male gender	863 (76.2)	618 (77.1)	245 (74.2)	.31
Age, mean (SD)	62.8 (10.8)	63.2 (10.6)	61.2 (11.1)	.004**
Clinical characteristics				
Multi-vessel disease	613 (54.3)	438 (54.8)	175 (53.0)	.58
Cardiac history [c]	517 (46.7)	366 (46.7)	151 (46.5)	.93
Indication for PCI				.86
Stable angina/ Silent ischemia	519 (46.3)	367 (46.2)	152 (46.8)	
Unstable angina	370 (33.0)	268 (33.7)	102 (31.4)	
MI	219 (19.6)	152 (19.1)	67 (20.6)	
Hypertension	512 (47.2)	361 (46.5)	151 (46.5)	.49
Diabetes mellitus	198 (17.5)	141 (17.6)	75 (17.6)	.90
Family history of CAD	491 (45.3)	352 (45.4)	139 (45.0)	.91
Self-reported smoking	220 (20.3)	135 (17.4)	85 (27.5)	<.001***
BMI, mean (SD)	27.3 (4.4)	27.2 (4.3)	27.4 (4.7)	.63
Cardiac medication				
Aspirin	1098 (97.3)	776 (96.6)	322 (98.2)	.23
ACE-inhibitors	410 (36.3)	317 (39.6)	93 (28.4)	<.001***
Beta-blockers	857 (75.9)	617 (77.0)	240 (73.2)	.17
Calcium-antagonists	335 (29.7)	273 (34.1)	62 (18.9)	<.001***
Diuretics	112 (9.9)	83 (10.4)	29 (8.8)	.44
Oral nitrates	211 (18.7)	149 (18.6)	62 (18.9)	.91
Statins	1001 (88.7)	712 (88.9)	289 (88.1)	.71
Psychological characteristics				
Depression				
Dichotomous (HADS-D≥8)	257 (22.7)	163 (20.3)	94 (28.5)	.003**
Continuous, mean (SD)	4.6 (3.9)	4.3 (3.8)	5.2 (4.2)	.002**

Table 1. *Continued*

	Total sample (N=1132)	***Completers (n=802)***	***Drop-outs [b] (n=330)***	***p***
Anxiety				
Dichotomous (HADS-A≥8)	285 (25.2)	186 (23.2)	99 (30.0)	.017*
Continuous, mean (SD)	5.3 (3.8)	5.1 (3.7)	5.8 (4.2)	.009**
Type D personality	288 (25.5)	196 (24.5)	92 (28.0)	.22
Negative affectivity, mean (SD)	8.4 (6.5)	8.1 (6.3)	9.3 (6.9)	.005**
Social inhibition, mean (SD)	9.0 (6.4)	8.9 (6.5)	9.3 (6.3)	.38

*$p \leq .05$; ** $p \leq .01$; *** $p \leq .001$

[a] Results are presented as n (%) unless otherwise stated

[b] Patients who completed the questionnaires at baseline, but dropped out of the study at 12-months post-PCI.

[c] Previous myocardial infarction (MI), percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG) surgery

ACE = angiotensin converter enzyme, BMI = body mass index (kg/m^2), CAD = coronary artery disease, HADS-A = Hospital Anxiety and Depression Scale - Anxiety, HADS-D = Hospital Anxiety and Depression Scale - Depression

DISCUSSION

The current study extends previous research by showing that a healthy volunteer effect might also be applicable to completers versus drop-outs, with drop-outs being more likely to smoke, experiencing higher levels of psychological distress (i.e., anxiety, depression, and negative affectivity), and less often being prescribed some cardiac discharge medications. Although one previous study in post-MI patients and one population-based study demonstrated that drop-out during follow-up was associated with a higher mortality risk [15, 16], our results did not corroborate this finding. This discrepancy may be explained by the fact that previous studies used a larger study sample (2690 post-MI patients and 14.121 Civil Service workers, respectively) and differences in follow-up duration (3 and 14 years, respectively). An increased mortality risk has also been repeatedly observed among non-participants in population-based studies [7, 10, 13] and clinical trials [12, 14]. As only one previous study focused on systematic differences between completers and drop-outs in CAD, future studies on this topic are warranted.

Limitations of the current study must be acknowledged. First, although we had information on all-cause mortality, we had no information on other reasons for drop-out. Second, no information on left ventricular ejection fraction (LVEF) was collected, which is an important marker for disease severity in CAD [20]. However, we addressed possible differences in disease severity by comparing completers and drop-outs on multi-vessel

disease and cardiac history. Third, we were not able to compare completers and drop-outs on use of psychotropic medication, as information on this type of medication was not collected. Finally, the current study was single-center.

In conclusion, in the current study a possible attrition bias occurred, as drop-outs and completers differed systematically on some socio-demographic, clinical, and psychological baseline characteristics. Despite these differences, this did not translate into a poorer prognosis, as there were no differences in the mortality risk of completers versus drop-outs. In future prospective studies, using serial assessments of patient-reported outcomes, attention should be paid to attrition bias, and its possible impact on study results and implications should be discussed.

FUNDING
This research was in part supported with a VIDI grant (91710393) to Dr. Susanne S. Pedersen from the Netherlands Organization for Health Research and Development (ZonMW), The Hague, The Netherlands.

CONFLICT OF INTEREST
None declared.

REFERENCES

1. Denollet J, Pedersen SS, Vrints CJ, Conraads VM. Usefulness of Type D personality in predicting five-year cardiac events above and beyond concurrent symptoms of stress in patients with coronary heart disease. Am J Cardiol. 2006;97(7):970-3.
2. Roest AM, Martens EJ, Denollet J, de Jonge P. Prognostic association of anxiety post myocardial infarction with mortality and new cardiac events: A meta-analysis. Psychosom Med. 2010;72(6):563-9.
3. Meijer A, Conradi HJ, Bos EH, Thombs BD, van Melle JP, de Jonge P. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: A meta-analysis of 25 years of research. Gen Hosp Psychiatry. 2011;33(3):203-16.
4. Versteeg H, Spek V, Pedersen SS, Denollet J. Type D personality and health status in cardiovascular disease populations: A meta-analysis of prospective studies. Eur J Cardiovasc Prev Rehabil. 2011;19(6):1373-80.
5. Grande G, Romppel M, Barth J. Association between Type D personality and prognosis in patients with cardiovascular diseases: A systematic review and meta-analysis. Ann Behav Med. 2012;43(3):299-310.
6. Damen NL, Pelle AJ, Szabó BM, Pedersen SS. Symptoms of anxiety and cardiac hospitalizations at 12 months in patients with heart failure. J Gen Intern Med. 2012;27(3):345-50.
7. Jousilahti P, Salomaa V, Kuulasmaa K, Niemelä M, Vartiainen E. Total and cause specific mortality among participants and non-participants of population based health surveys: A comprehensive follow up of 54 372 Finnish men and women. J Epidemiol Commun Health. 2005;59(4):310-5.
8. Wolke D, Waylen A, Samara M, Steer C, Goodman R, Ford T, et al. Selective drop-out in longitudinal studies and non-biased prediction of behaviour disorders. Br J Psychiatry. 2009;195(3):249-56.
9. Hoeymans N, Feskens EJM, van den Bos GAM, Kromhout D. Non-response bias in a study of cardiovascular diseases, functional status and self-rated health among elderly men. Age Ageing. 1998;27(1):35-40.
10. Hara M, Sasaki S, Sobue T, Yamamoto S, Tsugane S. Comparison of cause-specific mortality between respondents and nonrespondents in a population-based prospective study: Ten-year follow-up of JPHC Study Cohort I. J Clin Epidemiol. 2002;55(2):150-6.
11. Hill A, Roberts J, Ewings P, Gunnell D. Non-response bias in a lifestyle survey. J Public Health. 1997;19(2):203-7.
12. van Bergen PFMM, Jonker JJC, Molhoek GP, van der Burgh PH, van Domburg RT, Deckers JW, et al. Characteristics and prognosis of non-participants of a multi-centre trial of long-term anticoagulant treatment after myocardial infarction. Int J Cardiol. 1995;49(2):135-41.
13. Veenstra MY, Friesema IHM, Zwietering PJ, Garretsen HFL, Knottnerus JA, Lemmens PHHM. Lower prevalence of heart disease but higher mortality risk during follow-up was found among nonrespondents to a cohort study. J Clin Epidemiol. 2006;59(4):412-20.
14. de Boer SPM, Lenzen MJ, Oemrawsingh RM, Simsek C, Duckers HJ, van der Giessen WJ, et al. Evaluating the 'all-comers' design: A comparison of participants in two 'all-comers' PCI trials with non-participants. Eur Heart J. 2011;32(17):2161-7.
15. Candido E, Kurdyak P, Alter DA. Item nonresponse to psychosocial questionnaires was associated with higher mortality after acute myocardial infarction. J Clin Epidemiol. 2011;64(2):213-22.
16. Ferrie JE, Kivimäki M, Singh-Manoux A, Shortt A, Martikainen P, Head J, et al. Non-response to baseline, non-response to follow-up and mortality in the Whitehall II cohort. Int J Epidemiol. 2009;38(3):831-7.
17. Demark-Wahnefried W, Bowen DJ, Jabson JM, Paskett ED. Scientific bias arising from sampling, selective recruitment, and attrition: The case for improved reporting. Cancer Epidemiol Biomarkers Prev. 2011;20(3):415-8.
18. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med. 1997;27(2):363-70.
19. Denollet J. DS14: Standard assessment of negative affectivity, social inhibition, and Type D personality. Psychosom Med. 2005;67(1):89-97.
20. Strik JJMH, Denollet J, Lousberg R, Honig A. Comparing symptoms of depression and anxiety as predictors of cardiac events and increased health care consumption after myocardial infarction. J Am Coll Cardiol. 2003;42(10):1801-7.

CHAPTER 10

Anti-depressant and anxiolytic medication use in patients treated with coronary artery bypass graft surgery versus percutaneous coronary intervention: A Danish nationwide population-based study

Damen NL, Brouwers CJ, Versteeg H, Christensen SB, Torp-Pedersen C, Gislason GH, Pedersen SS. Submitted for publication.

ABSTRACT

Background: Coronary artery bypass graft (CABG) surgery is considered the optimal revascularization strategy for patients with complex coronary artery disease (CAD), whereas in patients with less severe CAD percutaneous coronary intervention (PCI) is recommended. As a more invasive procedure may be associated with increased use of psychotropic medications, we compared antidepressant and anxiolytic medication use between patients treated with CABG or PCI, using data from the Danish Heart Registry.

Methods: All patients treated with a first-time CABG or PCI between 1999 and 2012 in Denmark were identified. Antidepressant and anxiolytic medication use was determined by claimed prescriptions up to 12 months post-index event. Analyses were conducted in the total sample and a propensity-score matched sample. In addition to statistical significance, clinical relevance was evaluated by calculating absolute risk differences (ARD's) and risk ratios (RR's).

Results: We identified 62.912 patients, of whom 10.347 (16.4%) were treated with CABG and 52.565 (83.6%) with PCI. After propensity-score matching, the use of antidepressants (particularly selective serotonin reuptake inhibitors (SSRI's)) was significantly higher in CABG patients at 6 and 12 months post-index event as compared with PCI patients, although no difference was found on anxiolytic medication use. ARD's ranged between 1.0-1.8%, with corresponding RR's ranging between 1.1-1.2.

Conclusion: CABG patients were more often than PCI patients prescribed antidepressants (in particular SSRI's) up to 12 months. Given the small ARD's and RR's, these differences did not seem to be clinically relevant, possibly reflecting comparable underlying psychological distress levels in CABG and PCI patients.

INTRODUCTION

Since its introduction in 1968, coronary artery bypass graft (CABG) surgery rapidly became the treatment of choice for patients with advanced coronary artery disease (CAD) needing revascularization [1]. When percutaneous coronary intervention (PCI) was introduced in 1977, this method was thought to be appropriate only for patients with single-vessel disease [2]. However, increased experience with PCI and improved technology expanded its use to patients with more complex CAD, such as multi-vessel disease and left main coronary disease [3].

The optimal revascularization strategy for CAD has been subject of some debate. Several randomized controlled trials have compared clinical outcomes between CABG and PCI patients, showing similar survival rates but higher repeated revascularization rates among patients treated with PCI with drug-eluting stents as compared with CABG surgery patients [3-7]. These findings were also confirmed in systematic reviews [8, 9] and recent meta-analyses [10, 11].

Little is known about potential differences in patient-centered outcomes, such as anxiety and depression, between CABG and PCI patients. Previous studies indicated that anxiety and depression are common in both CABG and PCI patients, with prevalence rates ranging from 20-50%, and are associated with increased cardiovascular morbidity and mortality [12-15] and impaired health-related quality of life [16, 17]. Psychotropic medications are widely used treatments for anxiety and depression, but to our knowledge no study to date has directly compared the prevalence of psychotropic medication use between CABG and PCI patients. Hence, the aim of the current study was to examine differences in antidepressant and anxiolytic medication use between CABG and PCI patients up to 12 months post-index event, using data from the Danish Heart Registry.

METHODS

Data sources

In Denmark, all citizens are registered with a unique and permanent civil registration number in the Central Population Register, which enables linkage of information at the individual level across different registers. In the current study, 3 nationwide administrative registers were used and linked at an anonymous and individual level:

1) The Danish Heart Register, which contains information on patients undergoing the following invasive cardiac procedures and thoracic surgeries: Coronary angiography (CAG), PCI, CABG, and valve surgeries. The procedures are classified according to the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures (NCSP) [18].

2) The Danish National Patient Register, which contains information on all hospitalizations in Denmark since 1978. Each hospitalization is registered with 1 primary diagnosis and, if appropriate, a secondary diagnosis according to the World Health Organization's International Classification of Diseases, 10th Revision (ICD-10) [19].
3) The Danish Register of Medicinal Product Statistics (or the Danish Prescription Register), which holds information on all prescriptions dispensed from Danish pharmacies since 1995. Each prescription is coded according to the international classification of pharmaceuticals (Anatomic Therapeutical Chemical (ATC) system) and includes information on dispensing date, strength, formulation, quantity dispensed, and affiliation of the physician issuing the prescription. As the Danish health care system partially reimburses prescribed medications, pharmacies are requested to register all dispensed prescriptions, ensuring complete registration nationwide [20].

Study population

Using the Danish Heart Registry, we identified all patients admitted to Danish hospitals who underwent a first-time CABG surgery or PCI between 1999 and 2012. Information on socio-demographic characteristics (i.e., gender, age, and marital status) was obtained from the Central Population Register, whereas information on clinical characteristics (i.e., smoking status and body mass index (BMI)) was obtained from the Danish Heart Registry. Charlson's comorbidity index was calculated based on information from the Danish National Patient Register and included information on 19 comorbidities (i.e., acute myocardial infarction (MI), AIDS, any tumor, cerebrovascular disease, congestive heart failure, chronic pulmonary disease, connective tissue disease, dementia, diabetes mellitus, diabetes mellitus with chronic complications, hemiplegia, leukemia, lymphoma, metastatic solid tumor, mild liver disease, moderate/severe liver disease, moderate/severe renal disease, peripheral vascular disease, and ulcer disease) [21].

ATC codes from the Danish Prescription Register were used to identify all prescriptions for aspirin (B01AA04), angiotensin-converting enzyme (ACE)-inhibitors (C09), beta-blockers (C07), calcium-antagonists (C08), clopidogrel (B01AC04), digoxin (C01AA05), loop diuretics (C03), statins (C10), spironolactone (C03), and thiazide diuretics (C03). In line with previous Danish studies [22, 23], baseline medication use was defined as at least 1 claimed prescription within 3 months post-index event to ensure equal time for all patients to claim prescriptions for new medications after hospitalization.

Antidepressant and anxiolytic medication use

ATC codes were also used to identify prescriptions for antidepressants (N06A) and anxiolytics (N05B). Five different types of antidepressants were identified, including selective serotonin reuptake inhibitors (SSRI's) (N06AB), tricyclic antidepressants (TCA's) (N06AA), serotonin and noradrenaline reuptake inhibitors (SNRI's) (N06AX), noradrenergic and specific serotonergic antidepressants (NaSSA's) (N06AX), and tetracyclic antidepressants (N06AX). With regard to anxiolytic medication use, 3 different types of anxiolytics were identified, including benzodiazepines (N05BA), diphenylmethan derivatives (N05BB), and azaspirodecanedion derivatives (N05BE). As for the cardiac medications, baseline antidepressant and anxiolytic medication use was defined as at least 1 claimed prescription within 3 months post-index event. Besides baseline use, information on antidepressant and anxiolytic medication use at 6 and 12 months post-index event was collected to get insight into the evolution of psychotropic medication use.

Ethics

The current study was approved by the Danish Data Protection Agency (Ref. No. 2007-58-0015 / I. suite no. 00916 GEH-2010-001). Retrospective register studies in which individual patients cannot be identified do not require ethical approval in Denmark.

Statistical analyses

Prior to analyses, antidepressants were categorized into 4 groups: 1) any antidepressant (including all different types of antidepressants), 2) SSRI's, 3) TCA's, and 4) other antidepressants (i.e., SNRI's, NaSSA's, and tetracyclic antidepressants). Anxiolytics were categorized into 3 groups: 1) any anxiolytic (including all different types of anxiolytics), 2) benzodiazepines, and 3) other anxiolytics (i.e., diphenylmethan derivatives and azaspirodecanedion derivatives).

In the total sample, group differences on baseline characteristics and antidepressant and anxiolytic categories between CABG and PCI patients were examined using the Chi-square test for nominal variables and Student's t-test for independent samples for continuous variables. Second, in order to enhance comparability between CABG and PCI patients, CABG and PCI patients were matched on the propensity score. The propensity score was calculated by using logistic regression analysis conditional on baseline characteristics, using the Greedy match algorithm on a 1:1 ratio [24]. Only matched controls were included in the analyses, preserving the case-group (CABG patients) as originally identified. To ensure that matching was successful, group differences on baseline characteristics between the matched CABG and PCI patients were examined using the Chi-square test for nominal variables and Student's t-test for independent samples for continuous variables. These same tests were also used to examine group differences on antidepressant and anxiolytic categories between the matched CABG and PCI patients.

All results were based on 2-tailed tests and a *p*-value <.05 was used to indicate statistical significance. Clinical relevance of the results was also evaluated using absolute risk differences (ARD's) and risk ratios (RR's). Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina) and STATA version 11.2 (StataCorp Inc., College Station, TX).

RESULTS

Patient characteristics

In the current study, a total of 62.912 patients were included, of whom 10.347 (16.4%) underwent a CABG surgery and 52.565 (83.6%) patients were treated with PCI. Patient characteristics for the total sample and stratified by treatment are presented in Table 1. CABG and PCI patients differed systematically on all baseline characteristics.

Table 1. Patient characteristics for the total sample and stratified by treatment [a]

	Total sample (N=62.912)	***CABG (n=10.347)***	***PCI (n=52.565)***	***p***
Socio-demographic characteristics				
Male gender	45810 (73.6)	8152 (78.8)	37658 (72.6)	<.001***
Age, mean (SD)	65.85 (11.4)	68.41 (9.3)	65.93 (11.7)	<.001***
Married	32951 (52.4)	5683 (54.9)	27268 (51.9)	<.001***
Clinical characteristics				
Smoking	17905 (28.5)	1761 (17.0)	16144 (30.7)	<.001***
Obesity [b]	12720 (20.2)	2430 (23.5)	10290 (19.6)	<.001***
Charlson's comorbidity index [c]				<.001***
0	26415 (42.0)	5508 (53.2)	20907 (39.8)	
1	26473 (42.1)	2773 (26.8)	23700 (45.1)	
2	4807 (7.6)	892 (8.6)	3915 (7.5)	
3	2550 (4.1)	588 (5.7)	1962 (3.7)	
4	1543 (2.5)	333 (3.2)	1210 (2.3)	
≥5	1124 (1.8)	253 (2.5)	871 (1.7)	

Table 1. *Continued*

	Total sample (N=62.912)	***CABG (n=10.347)***	***PCI (n=52.565)***	***p***
Cardiac medication use at baseline				
Aspirin	40757 (64.8)	6015 (58.1)	34742 (66.1)	<.001***
ACE-inhibitors	27027 (43.0)	4331 (41.9)	22696 (43.2)	.013*
Beta-blockers	39152 (62.2)	6015 (58.1)	33137 (63.0)	<.001***
Calcium-antagonists	11381 (18.1)	2216 (21.4)	9165 (17.4)	<.001***
Clopidogrel	40704 (64.7)	2194 (21.2)	38510 (73.3)	<.001***
Digoxin	1658 (2.7)	332 (3.2)	1353 (2.6)	<.001***
Loop diuretics	11233 (17.9)	3456 (33.4)	7777 (14.8)	<.001***
Statins	43684 (69.4)	6625 (64.0)	37059 (70.5)	<.001***
Spironolactone	3161 (5.0)	790 (7.6)	2371 (4.5)	<.001***
Thiazide diuretics	5927 (9.4)	1268 (12.3)	4659 (8.9)	<.001***

*$p \leq .05$; ** $p \leq .01$; ***$p \leq .001$

[a] Results are presented as n (%) unless otherwise stated

[b] BMI ≥30; [c] included information on 19 comorbidities: Acute myocardial infarction (MI), AIDS, any tumor, cerebrovascular disease, congestive heart failure, chronic pulmonary disease, connective tissue disease, dementia, diabetes mellitus, diabetes mellitus with chronic complications, hemiplegia, leukemia, lymphoma, metastatic solid tumor, mild liver disease, moderate/severe liver disease, moderate/severe renal disease, peripheral vascular disease, and ulcer disease

ACE = angiotensin-converting enzyme, BMI = body mass index (kg/m^2), CABG = coronary artery bypass graft, PCI = percutaneous coronary intervention

Differences in antidepressant medication use between CABG and PCI patients in the 12 months post-index event

Overall, the prevalence rate of antidepressant medication use increased over time in both CABG and PCI patients, with prevalence rates increasing from 8.6% at baseline to 13.0% at 12 months in CABG patients and 7.7% at 3 months to 12.1% at 12 months in PCI patients. Statistically significant differences emerged between CABG and PCI patients, with any antidepressant use at baseline, 6, and 12 months post-index event being significantly higher in CABG patients as compared with PCI patients. When looking at the different types of antidepressants, CABG patients were more often using SSRI's at baseline, 6, and 12 months post-index event as compared with PCI patients. The ARD's at the different time points ranged between .9–1.2%, with corresponding RR's ranging between 1.1-1.2 (Table 2).

Differences in anxiolytic medication use between CABG and PCI patients in the 12 months post-index event

Overall, the prevalence rate of anxiolytic medication use increased over time in both CABG and PCI patients, with prevalence rates increasing from 5.1% at baseline to 7.4% at 12 months in CABG patients and 5.2% at baseline to 8.1% at 12 months in PCI patients. Statistically significant differences emerged between CABG and PCI patients, with the use of any anxiolytic at 12 months being significantly lower in CABG patients as compared with PCI patients. When looking at the different types of anxiolytics, CABG patients were less likely to use benzodiazepines at 12 months post-index event as compared with PCI patients. At baseline, 6, and 12 months post-index event, CABG patients were more often using other anxiolytics as compared with PCI patients. The ARD's for any anxiolytic and benzodiazepines at the different time points ranged between -.9- -.7%, with corresponding RR's of .9. For other anxiolytics, the ARD's were .1% at the different time points. The corresponding RR's were rather large, ranging between 1.6-1.9, but with wide CI's (Table 2).

Table 2. Antidepressant and anxiolytic medication use for the total sample and stratified by treatment [a]

	Total sample (N=62.912)	*CABG (n=10.347)*	*PCI (n=52.565)*	*p*	*ARD*	*RR (95% CI)*
Any antidepressant [b]						
3 months	4956 (7.9)	888 (8.6)	4068 (7.7)	.004**	.9	1.1 (1.0-1.2)
6 months	6418 (10.2)	1133 (11.0)	5285 (10.1)	.006**	.9	1.1 (1.0-1.2)
12 months	7684 (12.2)	1346 (13.0)	6338 (12.1)	.007**	.9	1.1 (1.0-1.1)
SSRI's						
3 months	3303 (5.3)	621 (6.0)	2682 (5.1)	<.001***	.9	1.2 (1.1-1.3)
6 months	4397 (7.0)	811 (7.8)	3586 (6.8)	<.001***	1.0	1.1 (1.1-1.2)
12 months	5341 (8.5)	985 (9.5)	4356 (8.3)	<.001***	1.2	1.1 (1.1-1.2)
TCA's						
3 months	548 (.9)	84 (.8)	464 (.9)	.48	-.1	.9 (.7-1.2)
6 months	706 (1.1)	116 (1.1)	590 (1.1)	.99	0	1.0 (.8-1.2)
12 months	897 (1.4)	148 (1.4)	749 (1.4)	.97	0	1.0 (.8-1.2)
Other antidepressants [c]						
3 months	1572 (2.5)	257 (2.5)	1315 (2.5)	.92	0	1.0 (.9-1.1)
6 months	2094 (3.3)	342 (3.3)	1752 (3.3)	.89	0	1.0 (.8-1.2)
12 months	2635 (4.2)	421 (4.1)	2214 (4.2)	.51	-.1	1.0 (.9-1.1)
Any anxiolytic [d]						
3 months	3237 (5.2)	530 (5.1)	2707 (5.2)	.91	-.1	1.0 (.9-1.1)
6 months	4082 (6.5)	653 (6.3)	3429 (6.5)	.42	-.2	1.0 (.9-1.0)
12 months	5021 (8.0)	760 (7.4)	4261 (8.1)	.009**	-.7	.9 (.8-1.0)

Table 2. *Continued*

	Total sample (N=62.912)	*CABG (n=10.347)*	*PCI (n=52.565)*	*p*	*ARD*	*RR (95% CI)*
Benzodiazepines						
3 months	3170 (5.0)	514 (5.0)	2656 (5.1)	.72	-.1	1.0 (.9-1.1)
6 months	3986 (6.3)	628 (6.1)	3358 (6.4)	.22	-.3	1.0 (.9-1.0)
12 months	4882 (7.8)	728 (7.0)	4154 (7.9)	.003**	-.9	.9 (.8-1.0)
Other anxiolytics [e]						
3 months	84 (.1)	21 (.2)	63 (.1)	.034*	.1	1.7 (1.0-2.8)
6 months	123 (.2)	33 (.3)	90 (.2)	.002**	.1	1.9 (1.3-2.8)
12 months	183 (.3)	43 (.4)	140 (.3)	.010**	.1	1.6 (1.1-2.2)

*$p \leq .05$; ** $p \leq .01$; *** $p \leq .001$

[a] Results are presented as n (%)

[b] Including all different types of antidepressants: Selective serotonin reuptake inhibitors (SSRI's), tricyclic antidepressants (TCA's), serotonin and noradrenaline reuptake inhibitors (SNRI's), noradrenergic and specific serotonergic antidepressants (NaSSA's), and tetracyclic antidepressants

[c] SNRI's, NaSSA's, and tetracyclic antidepressants

[d] Including all different types of anxiolytics: Benzodiazepines, diphenylmethan derivatives, and azaspirodecanedion derivatives

[e] Diphenylmethan derivatives, azaspirodecanedion derivatives

ARD = Absolute risk difference (%), RR = Risk ratio

CABG = coronary artery bypass graft, PCI = percutaneous coronary intervention

Differences in antidepressant and anxiolytic medication use in a propensity-score matched sample of CABG and PCI patients, up to 12 months post-index event

After propensity score matching, a total of 14.042 patients were included, equally divided between 7.021 CABG and 7.021 PCI patients, respectively. Baseline characteristics were well balanced between CABG and PCI patients (Table 3).

As for the total sample, we found an increase in antidepressant and anxiolytic medication use over time in both CABG and PCI patients in the matched sample. Significant differences emerged between CABG and PCI patients, with the use of any antidepressant at 6 and 12 months post-index event being significantly higher in CABG patients as compared with PCI patients. When looking at the different types of antidepressants, CABG patients were more often using SSRI's at 6 and 12 months post-index event as compared with PCI patients. The ARD's at the different time points ranged between 1.0-1.8%, with corresponding RR's ranging between 1.1-1.2. There were no statistically significant differences in anxiolytic medication use between CABG and PCI patients (Table 4).

Table 3. Patient characteristics for the total propensity-score matched sample and stratified by treatment [a]

	Total sample (N=14.042)	***CABG (n=7.021)***	***PCI (n=7.021)***	***p***
Socio-demographic characteristics				
Male gender	10753 (76.6)	5377 (76.6)	5376 (76.6)	.98
Age, mean (SD)	68.06 (10.1)	67.93 (9.5)	68.18 (10.7)	.14
Married	7461 (53.1)	3743 (53.3)	3718 (53.0)	.67
Clinical characteristics				
Smoking	2822 (20.1)	1406 (20.0)	1416 (20.2)	.83
Obesity [b]	3128 (22.3)	1571 (22.4)	1557 (22.2)	.78
Charlson's comorbidity index [c]				.032*
0	7364 (52.4)	3640 (51.8)	3724 (53.0)	
1	4021 (28.6)	1980 (28.2)	2041 (29.1)	
2	1148 (8.2)	627 (8.9)	521 (7.4)	
3	716 (5.1)	365 (5.2)	351 (5.0)	
4	440 (3.1)	243 (3.5)	197 (2.8)	
≥5	353 (2.5)	166 (2.4)	187 (2.7)	

Table 3. *Continued*

	Total sample (N=14.042)	***CABG (n=7.021)***	***PCI (n=7.021)***	***p***
Cardiac medication use at baseline				
Aspirin	7322 (52.1)	3624 (51.6)	3698 (52.7)	.21
ACE-inhibitors	5320 (37.9)	2637 (37.6)	2683 (38.2)	.42
Beta-blockers	7350 (52.3)	3708 (52.8)	3642 (51.9)	.27
Calcium-antagonists	2702 (19.2)	1334 (19.0)	1368 (19.5)	.47
Clopidogrel	4495 (32.0)	2194 (31.3)	2301 (32.8)	.05
Digoxin	410 (2.9)	209 (3.0)	201 (2.9)	.69
Loop diuretics	3293 (23.5)	1748 (24.9)	1545 (22.0)	<.001***
Statins	8086 (57.6)	3987 (56.8)	4099 (58.4)	.056
Spironolactone	836 (6.0)	443 (6.3)	393 (5.6)	.075
Thiazide diuretics	1383 (9.9)	706 (10.1)	677 (9.6)	.41

*$p \leq .05$; ** $p \leq .01$; *** $p \leq .001$

[a] Results are presented as n (%) unless otherwise stated

[b] BMI ≥30

[c] included information on 19 comorbidities: Acute myocardial infarction (MI), AIDS, any tumor, cerebrovascular disease, congestive heart failure, chronic pulmonary disease, connective tissue disease, dementia, diabetes mellitus, diabetes mellitus with chronic complications, hemiplegia, leukemia, lymphoma, metastatic solid tumor, mild liver disease, moderate/severe liver disease, moderate/severe renal disease, peripheral vascular disease, and ulcer disease

ACE = angiotensin-converting enzyme, BMI = body mass index (kg/m^2), CABG = coronary artery bypass graft, PCI = percutaneous coronary intervention

Table 4. Antidepressant and anxiolytic medication use for the total propensity-score matched sample and stratified by treatment [a]

	Total sample (N=14.042)	*CABG (n=7.021)*	*PCI (n=7.021)*	*p*	*ARD*	*RR (95% CI)*
Any antidepressant [b]						
3 months	1062 (7.6)	556 (7.9)	506 (7.2)	.11	.7	1.1 (1.0-1.2)
6 months	1353 (9.6)	722 (10.3)	631 (9.0)	.009**	1.3	1.1 (1.0-1.3)
12 months	1586 (11.3)	859 (12.2)	727 (10.4)	<.001***	1.8	1.2 (1.1-1.3)
SSRI's						
3 months	734 (5.2)	384 (5.5)	350 (5.0)	.20	.5	1.1 (1.0-1.3)
6 months	952 (6.8)	510 (7.3)	442 (6.3)	.022*	1.0	1.2 (1.0-1.3)
12 months	1135 (8.1)	628 (8.9)	507 (7.2)	<.001***	1.7	1.2 (1.1-1.4)
TCA's						
3 months	113 (.8)	53 (.8)	60 (.9)	.51	-.1	.9 (.6-1.3)
6 months	143 (1.0)	70 (1.0)	73 (1.0)	.80	1.0	1.0 (.7-1.3)
12 months	181 (1.3)	89 (1.3)	92 (1.3)	.82	1.0	1.0 (.7-1.3)
Other antidepressants [c]						
3 months	321 (2.3)	169 (2.4)	152 (2.2)	.34	.2	1.1 (.9-1.4)
6 months	426 (3.0)	224 (3.2)	202 (2.9)	.28	.3	1.1 (.9-1.3)
12 months	530 (3.8)	277 (4.0)	253 (3.6)	.29	.4	1.1 (.9-1.3)
Any anxiolytic [d]						
3 months	683 (4.9)	353 (5.0)	330 (4.7)	.37	.3	1.1 (.9-1.2)
6 months	851 (6.1)	439 (6.3)	412 (5.9)	.34	.4	1.1 (.9-1.2)
12 months	1008 (7.2)	499 (7.1)	509 (7.3)	.74	-.2	1.0 (.9-1.1)

Table 4. *Continued*

	Total sample (N=14.042)	***CABG (n=7.021)***	***PCI (n=7.021)***	***p***	***ARD***	***RR (95% CI)***
Benzodiazepines						
3 months	667 (4.8)	345 (4.9)	322 (4.6)	.36	.3	1.1 (.9-1.2)
6 months	825 (5.9)	424 (6.0)	401 (5.7)	.41	.3	1.1 (.9-1.2)
12 months	970 (6.9)	477 (6.8)	493 (7.0)	.59	-.2	1.0 (.9-1.1)
Other anxiolytics [e]						
3 months	18 (.1)	9 (.1)	9 (.1)	1.0	0	1.0 (.4-2.5)
6 months	33 (.2)	18 (.3)	15 (.2)	.60	.1	1.5 (.6-2.4)
12 months	50 (.4)	27 (.4)	23 (.3)	.57	.1	1.3 (.7-2.0)

*$p \leq .05$; ** $p \leq .01$; *** $p \leq .001$

[a] Results are presented as n (%)

[b] Including all different types of antidepressants: Selective serotonin reuptake inhibitors (SSRI's), tricyclic antidepressants (TCA's), serotonin and noradrenaline reuptake inhibitors (SNRI's), noradrenergic and specific serotonergic antidepressants (NaSSA's), and tetracyclic antidepressants

[c] SNRI's, NaSSA's, and tetracyclic antidepressants

[d] Including all different types of anxiolytics: Benzodiazepines, diphenylmethan derivatives, and azaspirodecanedion derivatives

[e] Diphenylmethan derivatives, azaspirodecanedion derivatives

ARD = Absolute risk difference (%), RR = Risk ratio

CABG = coronary artery bypass graft, MI = myocardial infarction, PCI = percutaneous coronary intervention

DISCUSSION

To our knowledge, this is the first study to compare psychotropic medication use between CABG and PCI patients. Overall, the use of antidepressant and anxiolytic medications increased over time in both CABG and PCI patients. In the total sample, the use of antidepressants, and SSRI's in particular, was significantly higher in CABG patients at all time points as compared with PCI patients. The use of anxiolytics, and benzodiazepines in particular, was significantly higher in PCI patients at 12-months post-index event as compared with CABG patients, whereas the use of other anxiolytics was higher in CABG patients at all time points. After propensity-score matching, there was still a significant difference in antidepressant medication use between CABG and PCI patients, but not in anxiolytic medication use. However, given that corresponding ARD's and RR's were rather small, these statistically significant differences did not seem to be clinically relevant, possibly reflecting comparable levels of anxiety and depression up to 12 months post-index event.

The overall increase in antidepressant and anxiolytic medication use up to 12 months post-index event found in the current study is in line with findings from a previous study in post-MI patients, showing an increase in the rate of antidepressant prescription, and SSRI's in particular, over the past decade [25]. In the latter study, 7.8% of patients were prescribed antidepressants within 6 months post-MI, which is in line with the baseline prevalence rates found in the current study. Previous studies in CABG patients mainly reported on antidepressant medication use before surgery, indicating that 2.5-12% of patients are prescribed SSRI's prior to surgery [26-28]. As we did not take psychotropic medication use before revascularization into account, we cannot compare these prevalence rates with those of the current study. Our baseline prevalence rates of antidepressant and anxiolytic medication use in PCI patients were comparable to rates ranging between 6-13% reported in previous studies on psychological functioning post-PCI [29, 30].

So far, the efficacy of pharmacological treatment for psychological distress remains unclear. Results of pharmacological intervention trials for depression demonstrated that antidepressants could (modestly) reduce symptoms of depression in CAD patients [31-33], but this did not translate into enhanced survival [32]. Besides, cardiotoxic effects of antidepressants were reported, as in several studies antidepressant medication use before CABG surgery was associated with an increased risk for long-term mortality [26, 28] and rehospitalization [28]. In another study, use of SSRI's or SNRI's was associated with a higher risk for in-hospital morbidity but not with increased bleeding events or mortality after CABG surgery [27]. To date no studies have focused on potential differences in the impact of antidepressant and anxiolytic medication use on patient-reported and clinical outcomes between CABG and PCI patients, so future studies on this topic are warranted.

As indicated by the American Institute of Medicine in their recommendations for the optimal health care system in the 21st century, patient-centeredness is 1 of 6 criteria that should guide clinical trials, guidelines, and treatment decisions [34]. Current guidelines recommend that CABG surgery should be the treatment of choice for patients with complex CAD, such as three-vessel disease, left main coronary disease, and anatomically complex and extensive lesions, while PCI may be considered an alternative strategy in patients with less severe CAD [35]. The guidelines also recommend that risks and benefits of each procedure should be weighed in the decision-making process, taking also into account the patient baseline risk profile and patient preferences [3, 35]. Given that psychological distress is associated with an increased risk for cardiovascular morbidity and mortality [12-15] and impaired health-related quality of life [16, 17], it might be worthwhile to consider psychological consequences of each treatment strategy in the decision-making process in addition to clinical outcomes.

In the current study, we used antidepressant and anxiolytic medication use as a proxy for underlying levels of anxiety and depression. However, future studies are warranted to examine the congruence between psychological morbidity and psychotropic medication use in CABG and PCI patients, as the claimed prescriptions may not correspond with the actual underlying levels of psychological distress. Previous population-based studies have identified a mismatch between the prevalence of mental health problems and received treatment, with two thirds of patients not receiving pharmacological treatment for their mental problems [36-38]. In a recent study in implantable cardioverter defibrillator patients, this gap between the need for psychological treatment and actual delivery of treatment was also confirmed [39]. To our knowledge, no such study has been conducted in neither CABG nor PCI patients, although it warrants information on both clinical diagnoses of anxiety and depression and antidepressant and anxiolytic medication use.

The main strength of the current study is the completeness of the data and the generalizability of the results, with our sample comprising a nationwide unselected cohort of Danish CABG and PCI patients and data on antidepressant and anxiolytic medication use being complete. The data in the registries has been shown to be accurate [18-20]. Limitations of the current study should also be acknowledged. First, the registries do not include information on clinical diagnoses of anxiety and depression. The use of antidepressant and anxiolytic medication use as a proxy for anxiety and depression may imply bias, as the claimed prescriptions may not correspond with the actual underlying levels of psychological distress. Second, the use of claimed prescriptions as a proxy of medical treatment in the study population may imply bias as well, as the claimed prescriptions may not accurately reflect consumed medication. However, in Denmark the medications of interest are dispensed only with a valid prescription and all pharmacies must report every claimed prescription because of a national reimbursement scheme, which ensures

complete registration of dispensed drugs and diminishes the patient's incentive to obtain medications through other sources. Moreover, the Danish Prescription Register has been shown to be highly accurate, with concordance between drug dispensing and consumption likely to be high [20]. Third, we did not have information on indicators of disease severity, such as multi-vessel disease or left ventricular ejection fraction. Finally, generalizing these results to other health care systems and to other countries should be done with caution [40].

In conclusion, the current study showed that in both the total sample and a propensity-score matched cohort of CABG and PCI patients, CABG patients were more often being prescribed antidepressants, and SSRI's in particular, up to 12 months post-index event. After propensity-score matching, no significant differences were found in anxiolytic medication use between CABG and PCI patients. Given the small ARD's and RR's, the statistically significant differences found on antidepressant medication use did not seem to be clinically relevant, possibly reflecting comparable underlying psychological distress levels in CABG and PCI patients. As this is the first study to compare psychotropic medication use between CABG and PCI patients, future studies are warranted to replicate our findings and further investigate the clinical and psychological impact of both CABG and PCI in order to enhance patient-centered care.

FUNDING
Dr. Gislason is funded by an unrestricted clinical research scholarship from the Novo Nordisk Foundation.

CONFLICT OF INTEREST
None declared.

REFERENCES

1. Favaloro RG. Saphenous vein autograft replacement of severe segmental coronary artery occlusion: Operative technique. Ann Thorac Surg. 1968;5(4):334-9.
2. Grüntzig AR, Senning Å, Siegenthaler WE. Nonoperative dilatation of coronary-artery stenosis. N Engl J Med. 1979;301(2):61-8.
3. Mohr FW, Morice M, Kappetein AP, Feldman TE, Ståhle E, Colombo A, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. Lancet. 2013;381(9867):629-38.
4. Wu X, Chen Y, Liu H, Teirstein PS, Kirtane AJ, Ge C, et al. Comparison of long-term (4-year) outcomes of patients with unprotected left main coronary artery narrowing treated with drug-eluting stents versus coronary-artery bypass grafting. Am J Cardiol. 2010;105(12):1728-34.
5. Serruys PW, Onuma Y, Garg S, Vranckx P, de Bruyne B, Morice M, et al. 5-year clinical outcomes of the ARTS II (Arterial Revascularization Therapies Study II) of the sirolimus-eluting stent in the treatment of patients with multivessel de novo coronary artery lesions. J Am Coll Cardiol. 2010;55(11):1093-101.
6. Park S, Kim Y, Park D, Yun S, Ahn J, Song HG, et al. Randomized trial of stents versus bypass surgery for left main coronary artery disease. N Engl J Med. 2011;364(18):1718-27.
7. Boudriot E, Thiele H, Walther T, Liebetrau C, Boeckstegers P, Pohl T, et al. Randomized comparison of percutaneous coronary intervention with sirolimus-eluting stents versus coronary artery bypass grafting in unprotected left main stem stenosis. J Am Coll Cardiol. 2011;57(5):538-45.
8. Bravata DM, Gienger AL, McDonald KM, Sundaram V, Perez MV, Varghese R, et al. Systematic review: The comparative effectiveness of percutaneous coronary interventions and coronary artery bypass graft surgery. Ann Intern Med. 2007;147(10):703-16.
9. Hlatky MA, Boothroyd DB, Bravata DM, Boersma E, Booth J, Brooks MM, et al. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: A collaborative analysis of individual patient data from ten randomised trials. Lancet. 2009;373(9670):1190-7.
10. Yan TD, Padang R, Poh C, Cao C, Wilson MK, Bannon PG, et al. Drug-eluting stents versus coronary artery bypass grafting for the treatment of coronary artery disease: A meta-analysis of randomized and nonrandomized studies. J Thorac Cardiovasc Surg. 2011;141(5):1134-44.
11. Jang J, Choi K, Jin H, Seo J, Yang T, Kim D, et al. Meta-analysis of three randomized trials and nine observational studies comparing drug-eluting stents versus coronary artery bypass grafting for unprotected left main coronary artery disease. Am J Cardiol. 2012;110(10):1411-8.
12. Damen NL, Versteeg H, Boersma E, Serruys PW, van Geuns RJ, Denollet J, et al. Depression is independently associated with 7-year mortality in patients treated with percutaneous coronary intervention: Results from the RESEARCH registry. Int J Cardiol. 2012;167(6):2496-501.
13. Blumenthal JA, Lett HS, Babyak MA, White W, Smith PK, Mark DB, et al. Depression as a risk factor for mortality after coronary artery bypass surgery. Lancet. 2003;362(9384):604-9.
14. Connerney I, Sloan RP, Shapiro PA, Bagiella E, Seckman C. Depression is associated with increased mortality 10 years after coronary artery bypass surgery. Psychosom Med. 2010;72(9):874-81.
15. Tully PJ, Baker RA. Depression, anxiety, and cardiac morbidity outcomes after coronary artery bypass surgery: A contemporary and practical review. J Geriatr Cardiol. 2012;9(2):197-208.
16. Sullivan MD, LaCroix AZ, Spertus JA, Hecht J. Five-year prospective study of the effects of anxiety and depression in patients with coronary artery disease. Am J Cardiol. 2000;86(10):1135-8.
17. Pedersen SS, Denollet J, Spindler H, Ong ATL, Serruys PW, Erdman RAM, et al. Anxiety enhances the detrimental effect of depressive symptoms on health status following percutaneous coronary intervention. J Psychosom Res. 2006;61(6):783-9.
18. Abildstrøm SZ, Madsen M. The Danish Heart Register. Scand J Publ Health. 2011;39(7 suppl):46-9.
19. Andersen TF, Madsen M, Jørgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. Dan Med Bull. 1999;46(3):263-8.
20. Gaist D, Sørensen HT, Hallas J. The Danish prescription registries. Dan Med Bull. 1997;44(4):445-8.
21. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sørensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. BMC Med Res Methodol. 2011;11:83.

22. Bonde L, Sorensen R, Fosbøl EL, Abildstrøm SZ, Hansen PR, Kober L, et al. Increased mortality associated with low use of clopidogrel in patients with heart failure and acute myocardial infarction not undergoing percutaneous coronary intervention: A nationwide study. J Am Coll Cardiol. 2010;55(13):1300-7.
23. Sørensen R, Abildstrøm SZ, Hansen PR, Hvelplund A, Andersson C, Charlot M, et al. Efficacy of post-operative clopidogrel treatment in patients revascularized with coronary artery bypass grafting after myocardial infarction. J Am Coll Cardiol. 2011;57(10):1202-9.
24. D'Agostino RB. Propensity scores in cardiovascular research. Circulation. 2007;115(17):2340-3.
25. Benazon NR, Mamdani MM, Coyne JC. Trends in the prescribing of antidepressants following acute myocardial infarction, 1993–2002. Psychosom Med. 2005;67(6):916-20.
26. Stenman M, Holzmann MJ, Sartipy U. Antidepressant use before coronary artery bypass surgery is associated with long-term mortality. Int J Cardiol. 2013;167(6):2958-62.
27. Tully PJ, Cardinal T, Bennetts JS, Baker RA. Selective serotonin reuptake inhibitors, venlafaxine and duloxetine are associated with in hospital morbidity but not bleeding or late mortality after coronary artery bypass graft surgery. Heart Lung Circ. 2012;21(4):206-14.
28. Xiong GL, Jiang W, Clare R, Shaw LK, Smith PK, Mahaffey KW, et al. Prognosis of patients taking selective serotonin reuptake inhibitors before coronary artery bypass grafting. Am J Cardiol. 2006;98(1):42-7.
29. Pedersen SS, Martens EJ, Denollet J, Appels A. Poor health-related quality of life is a predictor of early, but not late, cardiac events after percutaneous coronary intervention. Psychosomatics. 2007;48(4):331-7.
30. Pedersen SS, Smith ORF, de Vries J, Appels A, Denollet J. Course of anxiety symptoms over an 18-month period in exhausted patients post percutaneous coronary intervention. Psychosom Med. 2008;70(3):349-55.
31. Lespérance F, Frasure-Smith N, Koszycki D, Laliberte MA, van Zyl LT, Baker B, et al. Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease: The Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial. J Am Med Assoc. 2007;297(4):367-79.
32. Glassman AH, O'Connor CM, Califf RM, Swedberg K, Schwartz P, Bigger JT, et al. Sertraline treatment of major depression in patients with acute MI or unstable angina. J Am Med Assoc. 2002;288(6):701-9.
33. Honig A, Kuyper AMG, Schene AH, van Melle JP, de Jonge P, Tulner DM, et al. Treatment of post-myocardial infarction depressive disorder: A randomized, placebo-controlled trial with mirtazapine. Psychosom Med. 2007;69(7):606-13.
34. Institute of Medicine report. Crossing the Quality Chasm: A New Health System for the 21st Century. The National Academies Press; 2001.
35. Kushner FG, Hand M, Smith Jr SC, King Iii SB, Anderson JL, Antman EM, et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update): A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2009;54(23):2205-41.
36. Alonso J, Lépine JP. Overview of key data from the European Study of the Epidemiology of Mental Disorders (ESEMeD). J Clin Psychiatry. 2007;68 Suppl 2:3-9.
37. Collins KA, Westra HA, Dozois DJA, Burns DD. Gaps in accessing treatment for anxiety and depression: Challenges for the delivery of care. Clin Psychol Rev. 2004;24(5):583-616.
38. Lecrubier Y. Widespread underrecognition and undertreatment of anxiety and mood disorders: Results from 3 European studies. J Clin Psychiatry. 2007;68 Suppl 2:36-41.
39. Hoogwegt MT, Kupper N, Theuns DAMJ, Zijlstra WP, Jordaens L, Pedersen SS. Undertreatment of anxiety and depression in patients with an implantable cardioverter-defibrillator: Impact on health status. Health Psychol. 2012;31(6):745-53.
40. Fosbøl EL, Peterson ED, Weeke P, Wang TY, Mathews R, Kober L, et al. Spousal depression, anxiety, and suicide after myocardial infarction. Eur Heart J. 2013;34(9):649-56.

CHAPTER 11 General discussion

Coronary artery disease (CAD), generally caused by atherosclerosis, is the leading cause of death in the Western world and refers to abnormalities in the coronary arteries that facilitate the supply of blood and oxygen to the heart [1, 2]. Due to plaque growth inside the lumen of coronary arteries, they may become narrowed, which may lead to ischemic chest pain (i.e., angina pectoris). If a coronary artery becomes fully blocked due to plaque rupture and the subsequent formation of thrombosis, this may result in an acute coronary syndrome (ACS), such as myocardial infarction (MI) [1, 2]. In patients with CAD, coronary revascularization, medication, *or* a combination are the mainstays of treatment to restore coronary blood flow. Coronary artery bypass graft (CABG) surgery and percutaneous coronary intervention (PCI) comprise the 2 primary means of coronary revascularization [3, 4].

Over the past decades, interest has increased in the role of psychological factors in the onset and progression of CAD, which has also led to the inclusion of psychological factors in the 2012 European Guidelines for Prevention of Cardiovascular Diseases of the European Society of Cardiology [5]. Psychological distress, such as anxiety and depression, is highly prevalent in CAD, affecting 1 in 4 patients, and has been linked to increased cardiovascular morbidity and mortality [6, 7] and poorer patient-reported outcomes, such as impaired health status and quality of life [8-10]. So far, the majority of studies on psychological distress in CAD have focused on post-MI, CABG, or general CAD patients. Although PCI is currently the most commonly used coronary revascularization procedure, few studies have focused on the patient perspective in PCI. Hence, little is known about the impact of psychological distress in PCI patients and whether it is similar to that reported in post-MI, CABG, or general CAD populations, or whether disease- and treatment-specific processes play a role in this context. The current dissertation extends previous research by focusing on the psychological well-being of patients treated with PCI, the impact of psychological distress on long-term prognosis, potential underlying mechanisms, and the occurrence and consequence of attrition bias in prospective cohort studies. In this chapter, the main findings of this dissertation will be discussed and their implications for future research and clinical practice will be outlined.

OVERVIEW AND DISCUSSION OF MAIN FINDINGS

Indications for PCI include MI, unstable angina pectoris, and stable angina pectoris [4]. Previous studies have demonstrated that indication for PCI is associated with different cardiovascular morbidity and mortality rates [11, 12], but little is known about the influence of indication for PCI on psychological distress [13]. In *Chapter 2,* we examined the association between indication for PCI and anxiety and depression levels in 791 patients in the first year post-PCI. Patients treated with PCI due to MI, unstable angina pectoris, or stable angina pectoris did not differ significantly on anxiety and depression levels. It is plausible that especially psychological factors related to the subjective experience of the cardiac event are predictive of psychological distress in the long-term rather than the nature of the event and objective measures of disease severity [14].

In *Chapter 3*, we reported on changes in anxiety and depression in 715 patients over a 12-month period post-PCI using an intra-individual approach, and examined possible demographic and clinical correlates of these changes. There was a decline in distress scores over time, with a mean individual change from baseline to 12 months of -.16 (±3.0) for anxiety and -.02 (±2.8) for depression. In linear regression analyses, only baseline anxiety and depression levels were significant correlates of individual change scores in anxiety and depression. In other words, the higher the baseline distress levels, the lower the change in anxiety and depression scores over the 12-month follow-up period. Secondary analyses showed that anxiety remained stable in 76% of patients and depression in 81%. A stable pattern of anxiety and depression up to 1 year post-index event has been demonstrated previously in other cardiac patients groups, including post-MI [15] and CABG patients [16].

Although substantial research has focused on the impact of psychological distress on prognosis in patients with CAD, there is a gap in our understanding of the impact of psychological distress on long-term prognosis (≥5 years). The paucity of studies in CAD patients that examined the impact of depression on long-term mortality has yielded mixed results [16-20]. The aim of *Chapter 4* was to examine the association between depression and long-term mortality in 1234 PCI patients. Given that there has been a tendency in the literature to focus on one psychological risk factor at a time, also called 'risk factor of the month approach' [21], we also examined whether the effect of depression on mortality was independent of anxiety and the distressed (Type D) personality (i.e., the combination of negative affectivity and social inhibition traits [22]). After a median follow-up of 7 years, depression was independently associated with a 1.6-fold increased risk for all-cause mortality (HR=1.63; 95%CI [1.05-2.71], *p*=.038), after adjusting for relevant socio-demographic and clinical characteristics, anxiety, and Type D personality. Neither anxiety nor Type D personality were associated with mortality.

In contrast to the vast amount of research focusing on the impact of negative emotions on CAD outcomes, the role of positive emotions has received less attention [23, 24]. Studies focusing on anhedonia (i.e., reduced positive affect) have shown that anhedonia is associated with a higher risk for mortality and adverse cardiac events up to 2 years follow-up [23, 25]. In *Chapter 5*, results on the impact of anhedonia on long-term mortality in 1206 PCI patients were presented. After a median follow-up of 7 years, anhedonia was independently associated with a 1.5-fold increased risk for all-cause mortality (HR=1.51; 95%CI [1.03-2.22], *p*=.036), after adjusting for socio-demographic and clinical characteristics, and negative and relaxed affect. This study extends previous research by showing that anhedonia is not only associated with short-term but also with long-term prognosis in CAD, independent of negative affect. This supports the notion that positive and negative affect are not merely opposites on the same continuum [26].

Medical explanations, such as differences in medication prescriptions [27, 28], do not provide a clear understanding of the better survival rates reported in overweight or obese CAD patients, a phenomenon referred to as the "obesity paradox" [27, 28]. Impaired health status has been linked to poor prognosis in CAD [29, 30], and a paucity of studies focused on the association between obesity and health status [31, 32], but the role of health status in the context of obesity and mortality in CAD has not yet been examined. Hence, in *Chapter 6* we pursued health status as a potential explanation for the obesity paradox. After a median follow-up of 7 years, overweight but not obesity was significantly associated with a 40% *lower* risk for all-cause mortality in 1019 patients treated with PCI (HR=.60; 95%CI [.42-.86], *p*=.005). Health status did not seem to play a role in explaining the obesity paradox, as after adding the health status domains to the multivariable Cox regression model, the association between overweight and mortality remained unchanged.

Both Type D personality and dysfunctional parenting styles, like overprotection or coldness, have been associated with anxiety and depression [13, 33]. As parenting styles have been related to personality development [34, 35], dysfunctional parenting styles may also be associated with Type D personality, which in turn may increase the risk for anxiety and depression. Hence, the aim of *Chapter 7* was to examine whether remembered parenting was associated with anxiety and depression in cardiac patients and whether Type D personality mediated this relationship. To examine whether the effects differed between stages of heart disease, we used 2 cohorts of patients, namely 435 patients treated with PCI and 123 congestive heart failure patients. In both cohorts, remembered parenting was significantly associated with higher anxiety and depression levels and with Type D personality. In multivariable linear regression analyses, Type D personality accounted for 25-29% of the variance in anxiety and 23-46% of the variance in depression, while

remembered parenting was no longer significantly associated with these domains. Sobel tests and bootstrapping confirmed that Type D personality mediated the relationship between remembered parenting and anxiety and depression in both PCI and congestive heart failure patients.

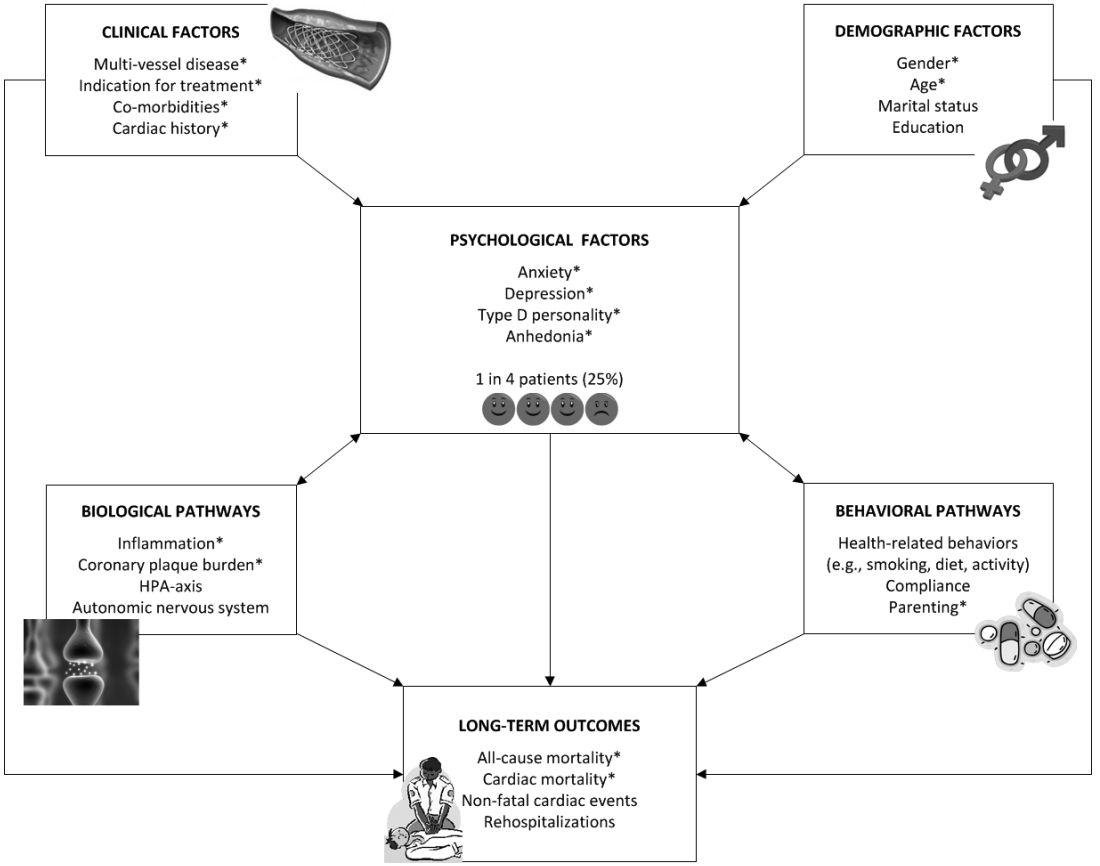
Chapter 8 elaborated on inflammation and the extent of coronary plaque burden as potential mechanisms underlying the relationship between psychological distress and prognosis in 183 patients treated with PCI. There were consistent, although small, *inverse* associations between psychological distress and serum levels of C-reactive protein (CRP) and tumor-necrosis factor alpha (TNF-α). Further, anxiety and negative affectivity were inversely associated with IVUS-derived coronary plaque burden. These findings are counterintuitive, as increased levels of distress were related to *lower* levels of inflammatory markers and coronary plaque burden. There were neither statistically significant associations between depression and inflammatory biomarkers nor between depression and coronary plaque burden. Overall, these results do not support increased inflammation and the extent of coronary plaque burden as likely mechanisms underlying the relationship between psychological distress and prognosis in PCI patients. Possibly, other biological (e.g., altered activity of the autonomic nervous system [36, 37]) or behavioral (e.g., less optimal health related behaviors [36, 38, 39]) mechanisms might provide a more robust explanation for this link.

In *Chapter 9,* the possible occurrence and consequence of attrition bias was investigated in a prospective cohort study in 1132 PCI patients. At 12 months follow-up, 71% of patients were classified as completers and 29% as drop-outs. A possible attrition bias occurred, as we observed significant differences in socio-demographic, clinical, and psychological baseline characteristics between completers and drop-outs. Drop-outs were younger, more likely to smoke, but less often prescribed some cardiovascular medications, including calcium-antagonists and ACE-inhibitors as compared with completers. Drop-outs also more often had depression, anxiety, and negative affectivity, as compared with completers. In post-MI patients and the general population, drop-out during follow-up has been associated with a higher mortality risk [40, 41], while our results found no support for this notion after a median follow-up of 4 years. In future prospective studies, using serial assessments of patient-reported outcomes, attention should be paid to attrition bias, and its possible impact on study results and implications should be discussed.

As aforementioned, besides PCI, CABG surgery is a common coronary revascularization procedure [3, 4]. Little is known about potential differences in patient well-being between CABG and PCI patients. A more invasive procedure may be associated with increased use of psychotropic medications. Hence, the aim of *Chapter 10* was to prospectively examine differences in antidepressant and anxiolytic medication use between CABG and PCI patients up to 12 months post-index event, using data from the national Danish Heart Registry. In this study, a total of 62.912 patients was included, of whom 10.347 (16%) underwent a CABG surgery and 52.565 (84%) patients were treated with PCI. In both the total sample and a propensity-score matched cohort of CABG and PCI patients, CABG patients were more often being prescribed antidepressants, and selective serotonin reuptake inhibitors (SSRI's) in particular, up to 12 months post-index event. After propensity-score matching, no significant differences were found in anxiolytic medication use between CABG and PCI patients. Given that corresponding absolute risk differences (ARD's) and risk ratios (RR's) were rather small, the statistically significant differences found on antidepressant medication use did not seem to be clinically relevant, possibly reflecting comparable underlying psychological distress levels in CABG and PCI patients, up to 12 months post-index event.

Figure 1 provides a conceptual model of the relationships between socio-demographic, clinical, and psychological factors, and long-term outcomes, as discussed in the current dissertation and previous studies. Taken together, the findings of this dissertation suggest that there is more to PCI than just coronary arteries, and that it seems worthwhile to take the patient perspective into account in order to optimize the management and care of PCI patients in clinical practice. Specific suggestions and recommendations for future research will be outlined.

Figure 1. Conceptual model of the relationships between demographic, clinical, and psychological factors, and long-term outcomes in PCI patients



OPTIMALIZATION OF THE MANAGEMENT AND CARE OF PCI PATIENTS

Identification of patients with a high-risk psychological profile

As presented in this dissertation, psychological distress, such as anxiety, depression, and Type D personality, is prevalent in 24-29% of PCI patients *(Chapters 4, 5, 8, and 9),* which is comparable to average rates reported in recent meta-analyses in post-MI [6, 7] and general CAD patients [42]. In about 80% of PCI patients, levels of anxiety and depression remain stable over time and seem to be best predicted by baseline distress levels *(Chapter 3)* rather than by objective measures of disease severity, such as indication for PCI *(Chapter 2)*. The current dissertation also indicated that psychological distress is related to long-term prognosis in addition to short-term prognosis, as both depression and anhedonia were associated with a 1.5-fold increased risk for 7-year mortality, after adjusting for baseline characteristics and other psychological risk factors *(Chapters 4 and 5)*. Hence, there is a need for the identification and monitoring of patients at high-risk for psychological distress, to provide them with appropriate treatment in order to reduce their psychological distress levels. The 2012 European Guidelines for Prevention of Cardiovascular Diseases of the European Society of Cardiology state that patients with established CAD but also those at risk for incident CAD should be screened for psychological distress factors, such as anxiety, depression, and Type D personality [5].

With regard to depression, there is an ongoing debate whether routine screening for depression in CAD patients should be implemented in clinical practice [43-50]. In 2008, an advisory from the American Heart Association (AHA) recommended routine depression screening in all CAD patients, using a 2-step screening protocol including the 2-item Patient Health Questionnaire (PHQ-2) and the 9-item Patient Health Questionnaire (PHQ-9) [48]. However, based on results from systematic reviews, to date there is no evidence that routine screening for depression – in combination with appropriate treatment when indicated - improves depression and clinical outcomes [43, 50]. Since the AHA advisory, studies have examined the feasibility of implemented screening as part of standard clinical practice, with mixed results [45, 46]. For example, an evaluation of the implementation of the 2-step screening protocol in MI patients showed that feasibility of the protocol was low, as about 25% of eligible patients did not get screened, and only had a modest impact on depression recognition [46].

Cardiac rehabilitation

Although there is no hard evidence that routine screening for psychological distress may result in improved CAD outcomes, appropriate monitoring and treatment of patients at high-risk for psychological distress seems important, given the high prevalence of distress in CAD patients and its risk associated with morbidity and mortality [6, 7].

In standard clinical practice, cardiac rehabilitation comprises an important part of the armamentarium of secondary prevention options for MI and coronary revascularization patients, combining exercise training with risk factor modification and psychological counseling [51, 52]. The beneficial effects of CR are unequivocal, as CR is associated with reductions in cardiovascular morbidity and mortality [53, 54] as well as improved patient-reported outcomes, such as anxiety, depression, and quality of life [53, 55, 56]. In several national guidelines, CR is included as a class I indication for post-MI or coronary revascularization patients [4, 57-59], and according to the current performance measures for CR, all patients hospitalized for a cardiac event, including MI, CABG, and PCI, should be referred to CR before hospital discharge [51]. Nevertheless, CR remains widely under-utilized, with overall referral rates ranging between 30-60% [60, 61] and over 50% of patients referred to CR not enrolling in the program [62, 63].

Previous studies have shown that participation rates are particularly low in patients treated with PCI, with PCI patients being about half as less likely to attend CR as compared with CABG or MI patients [64, 65] and with over one third of patients not being referred to CR [66]. There could be several reasons for the low attendance rates of PCI patients. First, it is possible that the very short hospital stay of PCI patients (i.e., 1-3 days) reduces the opportunity for arranging a referral to an outpatient CR program. Second, both patients and physicians may believe that standard CR programs are unnecessary for PCI patients, due to the less invasive, non-surgical nature of the procedure and patients often experiencing improved functional status immediately after PCI [65, 67]. However, findings from the current dissertation indicate that psychological distress is highly prevalent in patients treated with PCI and associated with poorer long-term prognosis *(Chapters 4, 5, 8, and 9)*, emphasizing the need for appropriate follow-up care for this specific patient group.

Besides low referral and attendance rates, high drop-out rates of 20-50% have been reported in CR programs [68, 69]. Patients not completing CR seem to be more likely to be depressed or anxious and report poorer quality of life as compared to patients completing CR [68-70]. In order to increase CR adherence and to improve outcomes for distressed CAD patients, initial screening for psychological distress upon admission to CR, monitoring of distress, and referral to appropriate psychological care if indicated may be paramount [68, 71].

Treatment of psychological distress

A variety of treatments have been suggested to target psychological distress in CAD patients, including both psychological and pharmacological treatments. Cognitive-behavioral therapy (CBT) is one of the mainstays of psychological treatment, and aims to identify and challenge negative automatic cognitions and behaviors [72]. Both the

Enhancing Recovery in Coronary Heart Disease patients (ENRICHD) randomized trial and the EXhaustion Intervention Trial (EXIT) demonstrated that CBT was associated with a modest reduction in psychological distress and improved social support in CAD patients, but this did not translate into a better prognosis [73, 74]. However, the more recent Secondary Prevention in Uppsala Primary Health Care Project (SUPRIM) showed that a 1-year CBT program reduced the risk for recurrent cardiovascular events [75]. Inconsistent results have also been reported from pharmacological intervention trials for depression, indicating that antidepressants could modestly reduce symptoms of depression in CAD patients [76, 77] but with no associated survival benefits [76]. The Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial evaluated the efficacy of combined antidepressant and psychological treatment, showing that antidepressant therapy with citalopram (i.e., SSRI) was associated with a reduction in depression scores, but there was no added value of short-term interpersonal psychotherapy over clinical management [78].

A lesson to be learned from these trials is that one size fits some but not all patients. Hence, more recently developed psychological intervention trials, such as the Coronary Psychosocial Evaluation Studies (COPES) and the Bypassing the Blues trial [79, 80], aimed to address several potential reasons for previous trials having shown modest to negligible results. One way forward may be to build in a 3-month observation period after an acute cardiac event to eliminate patients whose depressive symptoms might spontaneously remit due to symptoms being a reaction to an acute event. Second, in these recent trials interventions were tailored to patients' individual needs and preferences, allowing patients to choose between several treatment options. Further, a stepped-care approach was adopted, with symptom severity being reviewed regularly and depression treatment being adjusted when indicated. Finally, these trials used a collaborative care approach, with trained non-physician "care managers" closely monitoring patients' response to treatment, in close collaboration with the clinical management team [79, 80]. These patient-tailored, collaborative, stepped-care approaches led to significant improvements in depressed mood and health status [81, 82], a substantial improvement in satisfaction with depression care [82], and a promising reduction in major adverse cardiac events (i.e., non-fatal MI or hospitalization for unstable angina pectoris) and all-cause mortality [82].

RECOMMENDATIONS FOR CLINICAL PRACTICE AND FUTURE RESEARCH

Over the past decades, incorporation of the patient perspective into research and clinical practice has gained increased importance. As indicated by the American Institute of Medicine in their recommendations for an optimal health care system in the 21st century, patient-centeredness is 1 of 6 criteria that should guide clinical trials, guidelines, and treatment decisions [83]. The findings from the current dissertation extend previous research by indicating that psychological distress is prevalent in about 1 in 4 patients treated with PCI and associated with poorer long-term prognosis. In the majority of patients, levels of distress remain stable over time and seem to be best predicted by baseline distress levels rather than by objective measures of disease severity, such as indication for PCI. Hence, it is important that clinicians take into account the patient perspective in this specific CAD subgroup and focus on the early identification of patients at high-risk for psychological distress by means of screening and monitoring, and hereby looking beyond factors related to disease severity and treatment. Follow-up care for PCI patients should be tailored to patients' individual needs and preferences. Clinicians should refer PCI patients to CR, monitor their adherence to the program, and address potential reasons for non-adherence. When indicated, adjunctive psychological treatment should be provided (Table 1).

In addition to recommendations for clinical practice, Table 1 further outlines recommendations for future research. Future large-scale randomized controlled trials are needed to evaluate the benefit of screening for psychological distress in CAD, as it is still unclear whether routine screening (combined with psychological treatment) results in improved levels of distress and clinical outcomes [43]. Despite this controversy, a patient-tailored, collaborative, stepped-care approach of psychological treatment seems one avenue to pursue, as promising results were found in the first trials evaluating these approaches for the treatment of depression. Future psychological intervention trials are needed to further examine the impact of these approaches on distress levels, quality of life, and clinical outcomes.

Besides depression, future trials should seek to broaden the scope by targeting other psychological factors, such as anxiety and Type D personality, as they have also been related to poorer prognosis in CAD [6, 42]. A recent psychological intervention trial in Dutch community residents specifically targeted Type D personality, showing that a mindfulness-based stress reduction intervention was associated with a significant decrease in both NA and SI dimensions [84]. As indicated in *Chapter 5,* anhedonia is also of importance in the context of CAD both for short- and long-term prognosis. Therefore, future psychological intervention trials and clinical practice should not only target the reduction of negative emotions, but also seek to enhance positive emotions. The first results in this area are

promising, with CBT having been shown to improve positive affect in older depressed patients at increased cardiovascular risk [85], and mindfulness-based stress reduction programs improving positive affect in medically ill patients [86].

Finally, the complex nature of psychological distress in the context of CAD warrants further investigation. Besides adopting a 'risk factor of the month approach' and examining the impact of one psychological risk factor at a time, also their co-occurrence seems worthwhile considering in future research, as risk factors tend to cluster together and may dispose patients to a higher risk as compared to the presence of a single factor [21, 87, 88]. Future research should also seek to unravel whether it is incident or recurrent distress that leads to the highest risk for morbidity and mortality. For example, it has been suggested that post-MI patients with a first episode of major depression had poorer survival than those with recurrent depressive episodes [89,90]. Lastly, it is important to enhance our understanding of the potential biological and behavioral pathways underlying the relationship between psychological distress and poorer prognosis in CAD, as this might point towards targets for secondary prevention.

Table 1. Recommendations for future patient-centered initiatives in PCI patients

Recommendations for clinical practice
• Incorporate the patient perspective
• Identify patients at high-risk for psychological distress – look beyond factors related to disease and treatment severity
• Refer patients to CR and monitor their treatment adherence
• Provide care tailored to patients' individual needs and preferences
• Focus on enhancing positive emotions in patients in addition to reducing distress
Recommendations for future research
• Evaluate the benefit of routine screening for psychological distress
• Evaluate patient-tailored, collaborative, stepped-care approaches to treatment for psychological distress
• Examine appropriate timing of psychological interventions
• Examine potential mechanisms that may explain the link between psychological distress and prognosis
• Examine the impact of clustering of psychological factors and incident versus recurrent distress on prognosis

CR = cardiac rehabilitation, PCI = percutaneous coronary intervention

LIMITATIONS AND STRENGTHS OF THE CURRENT DISSERTATION

Some limitations of the findings presented in the current dissertation should be acknowledged. First, although the majority of studies included in this dissertation had a prospective cohort design, in *Chapters 7 and 8* we report on cross-sectional data. The findings from these cross-sectional studies should be interpreted with caution, as the study design does not allow for causal inferences and generalizability of the study findings might be limited. Second, data on psychological distress was obtained from self-report questionnaires and therefore, common method variance may have contributed to the significant results. However, we only used validated and reliable questionnaires to assess the psychological constructs studied, which have been used frequently in different cardiovascular patient groups [7, 42]. Besides, even minimal symptoms of distress, as assessed by a questionnaire, have been shown to predict poorer prognosis [91]. Third, although a variety of psychological distress factors have been addressed in this dissertation, we were not able to cover the whole spectrum of psychological factors that may be of importance in patients with CAD, such as a clinical diagnosis of anxiety and depression or other personality traits. Fourth, the majority of studies presented in this dissertation had a single-center design.

Strengths of the studies presented in the current dissertation comprise the relatively large samples of patients treated with PCI, ranging from 183 to 1234 patients. In addition, in *Chapter 10* we present unique data on a nationwide unselected cohort of 62.912 Danish CABG and PCI patients. A second strength includes the information on long-term mortality as presented in *Chapters 4 and 5*. In these chapters, we were able to examine the association between psychological distress and all-cause mortality after a median follow-up of 7 years, whereas previous studies have mainly followed patients for up to 5 years. Third, we had information on a wide range of socio-demographic and clinical characteristics, allowing for adjustment for these potential confounders in multivariable analyses.

CONCLUSION

The findings of the current dissertation suggest that the question of whether there is more to PCI than just coronary arteries could be answered with a whole-hearted "Yes". Although PCI is considered to be a minimally invasive procedure, psychological distress is prevalent in about 25% of patients, tends to be stable over time, and is associated with poorer prognosis. Hence, in order to optimize the management and care of PCI patients in clinical practice, it is important to incorporate the patient perspective and focus on the early identification and monitoring of patients at high-risk for psychological distress, hereby looking beyond factors related to disease severity and treatment. It is crucial not only to acknowledge the low referral and participation rates of PCI patients to CR, but also to take action. This is particularly important given that patients with high distress levels are less likely to consent to participate and more likely to drop-out, while paradoxically they are likely to benefit the most. When indicated, adjunctive psychological care should be provided. Throughout the management and care of PCI patients, their voices should be heard and their individual needs and preferences should be taken into account.

REFERENCES

1. Scarborough P, Bhatnager P, Wickramasinghe K, Smolina K, Mitchell C, Rayner M. Coronary heart disease statistics 2010. UK: Britisch Heart Foundation; 2010.
2. National-Heart-Lung-and-Blood-Institute. What is coronary heart disease? Available at: http://www.nhlbi.nih.gov/health/health-topics/topics/cad. Accessed August 9, 2013.
3. Silber S, Albertsson P, Avilés FF, Camici PG, Colombo A, Hamm C, et al. Guidelines for percutaneous coronary interventions: The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. Eur Heart J. 2005;26(8):804-47.
4. Kushner FG, Hand M, Smith Jr SC, King Iii SB, Anderson JL, Antman EM, et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update): A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2009;54(23):2205-41.
5. Perk J, de Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J. 2012;33(13):1635-701.
6. Roest AM, Martens EJ, Denollet J, de Jonge P. Prognostic association of anxiety post myocardial infarction with mortality and new cardiac events: A meta-analysis. Psychosom Med. 2010;72(6):563-9.
7. Meijer A, Conradi HJ, Bos EH, Thombs BD, van Melle JP, de Jonge P. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: A meta-analysis of 25 years of research. Gen Hosp Psychiatry. 2011;33(3):203-16.
8. Lane D, Carroll D, Ring C, Beevers DG, Lip GYH. Mortality and quality of life 12 months after myocardial infarction: Effects of depression and anxiety. Psychosom Med. 2001;63(2):221-30.
9. Versteeg H, Spek V, Pedersen SS, Denollet J. Type D personality and health status in cardiovascular disease populations: A meta-analysis of prospective studies. Eur J Cardiovasc Prev Rehabil. 2011;19(6):1373-80.
10. Sullivan MD, LaCroix AZ, Spertus JA, Hecht J. Five-year prospective study of the effects of anxiety and depression in patients with coronary artery disease. Am J Cardiol. 2000;86(10):1135-8.
11. Hirsch A, Verouden NJW, Koch KT, Baan J, Henriques JPS, Piek JJ, et al. Comparison of long-term mortality after percutaneous coronary intervention in patients treated for acute ST-elevation myocardial infarction versus those with unstable and stable angina pectoris. Am J Cardiol. 2009;104(3):333-7.
12. de Feyter PJ, Serruys PW, Unger F, Beyar R, de Valk V, Milo S, et al. Bypass surgery versus stenting for the treatment of multivessel disease in patients with unstable angina compared with stable angina. Circulation. 2002;105(20):2367-72.
13. van Gestel YRBM, Pedersen SS, van de Sande M, de Jaegere PPT, Serruys PW, Erdman RAM, et al. Type-D personality and depressive symptoms predict anxiety 12 months post-percutaneous coronary intervention. J Affect Disord. 2007;103(1):197-203.
14. Whitehead DL, Strike P, Perkins-Porras L, Steptoe A. Frequency of distress and fear of dying during acute coronary syndromes and consequences for adaptation. Am J Cardiol. 2005;96(11):1512-6.
15. Kaptein KI, de Jonge P, van den Brink RHS, Korf J. Course of depressive symptoms after myocardial infarction and cardiac prognosis: A latent class analysis. Psychosom Med. 2006;68(5):662-8.
16. Blumenthal JA, Lett HS, Babyak MA, White W, Smith PK, Mark DB, et al. Depression as a risk factor for mortality after coronary artery bypass surgery. Lancet. 2003;362(9384):604-9.
17. Connerney I, Sloan RP, Shapiro PA, Bagiella E, Seckman C. Depression is associated with increased mortality 10 years after coronary artery bypass surgery. Psychosom Med. 2010;72(9):874-81.

18. Barefoot JC, Helms MJ, Mark DB, Blumenthal JA, Califf RM, Haney TL, et al. Depression and long-term mortality risk in patients with coronary artery disease. Am J Cardiol. 1996;78(6):613-7.
19. Herrmann C, Brand-Driehorst S, Buss U, Rüger U. Effects of anxiety and depression on 5-year mortality in 5057 patients referred for exercise testing. J Psychosom Res. 2000;48(4-5):455-62.
20. Parakh K, Thombs BD, Fauerbach JA, Bush DE, Ziegelstein RC. Effect of depression on late (8 years) mortality after myocardial infarction. Am J Cardiol. 2008;101(5):602-6.
21. Rozanski A, Blumenthal JA, Davidson KW, Saab PG, Kubzansky L. The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: The emerging field of behavioral cardiology. J Am Coll Cardiol. 2005;45(5):637-51.
22. Denollet J. DS14: Standard assessment of negative affectivity, social inhibition, and Type D personality. Psychosom Med. 2005;67(1):89-97.
23. Denollet J, Pedersen SS, Daemen J, de Jaegere P, Serruys PW, van Domburg RT. Reduced positive affect (anhedonia) predicts major clinical events following implantation of coronary-artery stents. J Intern Med. 2008;263(2):203-11.
24. Brummett BH, Boyle SH, Siegler IC, Williams RB, Mark DB, Barefoot JC. Ratings of positive and depressive emotion as predictors of mortality in coronary patients. Int J Cardiol. 2005;100(2):213-6.
25. Davidson KW, Burg MM, Kronish IM, Shimbo D, Dettenborn L, Mehran R, et al. Association of anhedonia with recurrent major adverse cardiac events and mortality 1 year after acute coronary syndrome. Arch Gen Psychiatry. 2010;67(5):480-8.
26. Tellegen A, Watson D, Clark LA. On the dimensional and hierarchical structure of affect. Psychol Sci. 1999;10(4):297-303.
27. Gruberg L, Mercado N, Milo S, Boersma E, Disco C, van Es GA, et al. Impact of body mass index on the outcome of patients with multivessel disease randomized to either coronary artery bypass grafting or stenting in the ARTS trial: The obesity paradox II? Am J Cardiol. 2005;95(4):439-44.
28. Steinberg BA, Cannon CP, Hernandez AF, Pan W, Peterson ED, Fonarow GC. Medical therapies and invasive treatments for coronary artery disease by body mass: The "obesity paradox" in the Get With The Guidelines database. Am J Cardiol. 2007;100(9):1331-5.
29. Mommersteeg PM, Denollet J, Spertus JA, Pedersen SS. Health status as a risk factor in cardiovascular disease: A systematic review of current evidence. Am Heart J. 2009;157(2):208-18.
30. Schenkeveld L, Pedersen SS, van Nierop JWI, Lenzen MJ, de Jaegere PPT, Serruys PW, et al. Health-related quality of life and long-term mortality in patients treated with percutaneous coronary intervention. Am Heart J. 2010;159(3):471-6.
31. Evangelista LS, Moser DK, Westlake C, Hamilton MA, Fonarow GC, Dracup K. Impact of obesity on quality of life and depression in patients with heart failure. Eur J Heart Fail. 2006;8(7):750-5.
32. Oreopoulos A, Padwal R, McAlister FA, Ezekowitz J, Sharma AM, Kalantar-Zadeh K, et al. Association between obesity and health-related quality of life in patients with coronary artery disease. Int J Obes. 2010;34(9):1434-41.
33. Denollet J, Smolderen KGE, van den Broek KC, Pedersen SS. The 10-item Remembered Relationship with Parents (RRP10) scale: Two-factor model and association with adult depressive symptoms. J Affect Disord. 2007;100(1–3):179-89.
34. Aron EN, Aron A, Davies KM. Adult shyness: The interaction of temperamental sensitivity and an adverse childhood environment. Pers Soc Psychol Bull. 2005;31(2):181-97.
35. Enns MW, Cox BJ, Larsen DK. Perceptions of parental bonding and symptom severity in adults with depression: Mediation by personality dimensions. Can J Psychiatry. 2000;45(3):263-8.
36. Carney RM, Freedland KE, Miller GE, Jaffe AS. Depression as a risk factor for cardiac mortality and morbidity: A review of potential mechanisms. J Psychosom Res. 2002;53(4):897-902.
37. Martens EJ, Nyklíček I, Szabó BM, Kupper N. Depression and anxiety as predictors of heart rate variability after myocardial infarction. Psychol Med. 2008;38(3):375-83.
38. Gilmour J, Williams L. Type D personality is associated with maladaptive health-related behaviours. J Health Psychol. 2012;17(4):471-8.

39. Dempe C, Jünger J, Hoppe S, Katzenberger M, Möltner A, Ladwig KH, et al. Association of anxious and depressive symptoms with medication nonadherence in patients with stable coronary artery disease. J Psychosom Res. 2013;74(2):122-7.
40. Candido E, Kurdyak P, Alter DA. Item nonresponse to psychosocial questionnaires was associated with higher mortality after acute myocardial infarction. J Clin Epidemiol. 2011;64(2):213-22.
41. Ferrie JE, Kivimäki M, Singh-Manoux A, Shortt A, Martikainen P, Head J, et al. Non-response to baseline, non-response to follow-up and mortality in the Whitehall II cohort. Int J Epidemiol. 2009;38(3):831-7.
42. Denollet J, Schiffer AA, Spek V. A general propensity to psychological distress affects cardiovascular outcomes. Circ Cardiovasc Qual Outcomes. 2010;3(5):546-57.
43. Thombs BD, Roseman M, Coyne JC, de Jonge P, Delisle VC, Arthurs E, et al. Does evidence support the American Heart Association's recommendation to screen patients for depression in cardiovascular care? An updated systematic review. PLoS One. 2013;8(1):e52654.
44. Ziegelstein RC, Thombs BD, Coyne JC, de Jonge P. Routine screening for depression in patients with coronary heart disease: Never mind. J Am Coll Cardiol. 2009;54(10):886-90.
45. Elderon L, Smolderen KG, Na B, Whooley MA. Accuracy and prognostic value of American Heart Association: Recommended depression screening in patients with coronary heart disease: Data from the Heart and Soul Study. Circ Cardiovasc Qual Outcomes. 2011;4(5):533-40.
46. Smolderen KG, Buchanan DM, Amin AA, Gosch K, Nugent K, Riggs L, et al. Real-world lessons from the implementation of a depression screening protocol in acute myocardial infarction patients: Implications for the American Heart Association depression screening advisory. Circ Cardiovasc Qual Outcomes. 2011;4(3):283-92.
47. Hasnain M, Vieweg WVR, Lesnefsky EJ, Pandurangi AK. Depression screening in patients with coronary heart disease: A critical evaluation of the AHA guidelines. J Psychosom Res. 2011;71(1):6-12.
48. Lichtman JH, Bigger JT, Blumenthal JA, Frasure-Smith N, Kaufmann PG, Lespérance F, et al. Depression and coronary heart disease: Recommendations for screening, referral, and treatment: A science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: Endorsed by the American Psychiatric Association. Circulation. 2008;118(17):1768-75.
49. Davidson KW, Kupfer DJ, Bigger JT, Califf RM, Carney RM, Coyne JC, et al. Assessment and treatment of depression in patients with cardiovascular disease: National Heart, Lung, and Blood Institute Working Group Report. Psychosom Med. 2006;68(5):645-50.
50. Thombs BD, de Jonge P, Coyne JC, Whooley MA, Frasure-Smith N, Mitchell AJ, et al. Depression screening and patient outcomes in cardiovascular care: A systematic review. J Am Med Assoc. 2008;300(18):2161-71.
51. Thomas RJ, King M, Lui K, Oldridge N, Pina IL, Spertus J. AACVPR/ACCF/AHA 2010 update: Performance measures on cardiac rehabilitation for referral to cardiac rehabilitation/secondary prevention services: Endorsed by the American College of Chest Physicians, the American College of Sports Medicine, the American Physical Therapy Association, the Canadian Association of Cardiac Rehabilitation, the Clinical Exercise Physiology Association, the European Association for Cardiovascular Prevention and Rehabilitation, the Inter-American Heart Foundation, the National Association of Clinical Nurse Specialists, the Preventive Cardiovascular Nurses Association, and the Society of Thoracic Surgeons. J Am Coll Cardiol. 2010;56(14):1159-67.
52. Wenger NK, Froelicher ES, Smith LK, Ades PA, Berra K, Blumenthal JA, et al. Cardiac rehabilitation: Clinical practice guideline 17. U.S. Department of Health and Human Services; 1995.
53. Rutledge T, Redwine LS, Linke SE, Mills PJ. A meta-analysis of mental health treatments and cardiac rehabilitation for improving clinical outcomes and depression among patients with coronary heart disease. Psychosom Med. 2013;75(4):335-49.
54. Clark AM, Hartling L, Vandermeer B, McAlister FA. Meta-analysis: Secondary prevention programs for patients with coronary artery disease. Ann Intern Med. 2005;143(9):659-72.

55. Lavie CJ, Milani RV. Cardiac Rehabilitation and exercise training in secondary coronary heart disease prevention. Prog Cardiovasc Dis. 2011;53(6):397-403.
56. Hevey D, McGee HM, Horgan J. Relationship of initial level of distress to changes in health-related quality of life during cardiac rehabilitation or usual care. Psychosom Med. 2007;69(8):793-7.
57. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE, et al. 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;61(23):e179-347.
58. Eagle KA, Guyton RA, Davidoff R, Edwards FH, Ewy GA, Gardner TJ, et al. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: Summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). J Am Coll Cardiol. 2004;44(5):e213-310.
59. Fraker TD, Fihn SD, Gibbons RJ, Abrams J, Chatterjee K, Daley J, et al. 2007 chronic angina focused update of the ACC/AHA 2002 guidelines for the management of patients with chronic stable angina: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines Writing Group to develop the focused update of the 2002 guidelines for the management of patients with chronic stable angina. J Am Coll Cardiol. 2007;50(23):2264-74.
60. Brown TM, Hernandez AF, Bittner V, Cannon CP, Ellrodt G, Liang L, et al. Predictors of cardiac rehabilitation referral in coronary artery disease patients: Findings from the American Heart Association's Get With The Guidelines Program. J Am Coll Cardiol. 2009;54(6):515-21.
61. Gravely-Witte S, Leung YW, Nariani R, Tamim H, Oh P, Chan VM, et al. Effects of cardiac rehabilitation referral strategies on referral and enrollment rates. Nat Rev Cardiol. 2010;7(2):87-96.
62. Roblin D, Diseker RA, Orenstein D, Wilder M, Eley M. Delivery of outpatient cardiac rehabilitation in a managed care organization. J Cardiopulm Rehabil. 2004;24(3):157-64.
63. Mazzini MJ, Stevens GR, Whalen D, Ozonoff A, Balady GJ. Effect of an American Heart Association Get With the Guidelines program-based clinical pathway on referral and enrollment into cardiac rehabilitation after acute myocardial infarction. Am J Cardiol. 2008;101(8):1084-7.
64. Suaya JA, Shepard DS, Normand SL, Ades PA, Prottas J, Stason WB. Use of cardiac rehabilitation by Medicare beneficiaries after myocardial infarction or coronary bypass surgery. Circulation. 2007;116(15):1653-62.
65. Worcester MU, Murphy BM, Mee VK, Roberts SB, Goble AJ. Cardiac rehabilitation programmes: Predictors of non-attendance and drop-out. Eur J Cardiovasc Prev Rehabil. 2004;11(4):328-35.
66. Aragam KG, Moscucci M, Smith DE, Riba AL, Zainea M, Chambers JL, et al. Trends and disparities in referral to cardiac rehabilitation after percutaneous coronary intervention. Am Heart J. 2011;161(3):544-51.e2.
67. Wenger NK. Rehabilitation of the coronary patient: A preview of tomorrow. J Cardiopulm Rehabil Prev. 1991;11(2):93-8.
68. McGrady A, McGinnis R, Badenhop D, Bentle M, Rajput M. Effects of depression and anxiety on adherence to cardiac rehabilitation. J Cardiopulm Rehabil Prev. 2009;29(6):358-64.
69. Lavie CJ, Milani RV. Adverse psychological and coronary risk profiles in young patients with coronary artery disease and benefits of formal cardiac rehabilitation. Arch Int Med. 2006;166(17):1878-83.
70. Glazer KM, Emery CF, Frid DJ, Banyasz RE. Psychological predictors of adherence and outcomes among patients in cardiac rehabilitation. J Cardiopulm Rehabil. 2002;22(1):40-6.
71. Herridge ML, Stimler CE, Southard DR, King ML. Depression screening in cardiac rehabilitation: AACVPR Task Force Report. J Cardiopulm Rehabil. 2005;25(1):11-3.
72. Beck JS. Cognitive therapy: Basics and beyond. New York, Guilford; 1995.
73. ENRICHD Investigators. Effects of treating depression and low perceived social support on clinical events after myocardial infarction. J Am Med Assoc. 2003;289(23):3106-16.

74. Appels A, Bar F, van der Pol G, Erdman R, Assman M, Trijsburg W, et al. Effects of treating exhaustion in angioplasty patients on new coronary events: Results of the randomized Exhaustion Intervention Trial (EXIT). Psychosom Med. 2005;67(2):217-23.
75. Gullikson M, Burell G, Vessby B, Lundin L, Toss H, Svardsudd K. Randomized controlled trial of cognitive behavioral therapy vs standard treatment to prevent recurrent cardiovascular events in patients with coronary heart disease: Secondary Prevention in Uppsala Primary Health Care project (SUPRIM). Arch Intern Med. 2011;171(2):134-40.
76. Glassman AH, O'Connor CM, Califf RM, Swedberg K, Schwartz P, Bigger JT, et al. Sertraline treatment of major depression in patients with acute MI or unstable angina. J Am Med Assoc. 2002;288(6):701-9.
77. Honig A, Kuyper AMG, Schene AH, van Melle JP, de Jonge P, Tulner DM, et al. Treatment of post-myocardial infarction depressive disorder: A randomized, placebo-controlled trial with mirtazapine. Psychosom Med. 2007;69(7):606-13.
78. Lespérance F, Frasure-Smith N, Koszycki D, Laliberte MA, van Zyl LT, Baker B, et al. Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease: The Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial. J Am Med Assoc. 2007;297(4):367-79.
79. Burg MM, Lesperance F, Rieckmann N, Clemow L, Skotzko C, Davidson KW. Treating persistent depressive symptoms in post-ACS patients: The project COPES phase-I randomized controlled trial. Contemp Clin Trials. 2008;29(2):231-40.
80. Rollman BL, Belnap BH, LeMenager MS, Mazumdar S, Schulberg HC, Reynolds CF. The Bypassing the Blues treatment protocol: Stepped collaborative care for treating post-CABG depression. Psychosom Med. 2009;71(2):217-30.
81. Rollman BL, Belnap BH, LeMenager MS, Mazumdar S, Houck PR, Counihan PJ, et al. Telephone-delivered collaborative care for treating post-CABG depression: A randomized controlled trial. J Am Med Assoc. 2009;302(19):2095-103.
82. Davidson KW, Rieckmann N, Clemow L, Schwartz JE, Shimbo D, Medina V, et al. Enhanced depression care for patients with acute coronary syndrome and persistent depressive symptoms: Coronary Psychosocial Evaluation Studies randomized controlled trial. Arch Int Med. 2010;170(7):600-8.
83. Institute of Medicine report. Crossing the Quality Chasm: A New Health System for the 21st Century. The National Academies Press; 2001.
84. Nykliček I, van Beugen S, Denollet J. Effects of mindfulness-based stress reduction on distressed (Type D) personality traits: A randomized controlled trial. J Behav Med. 2012;36(4):361-70.
85. Strachowski D, Khaylis A, Conrad A, Neri E, Spiegel D, Taylor CB. The effects of cognitive behavior therapy on depression in older patients with cardiovascular risk. Depress Anxiety. 2008;25(8):E1-E10.
86. Grossman P, Tiefenthaler-Gilmer U, Raysz A, Kesper U. Mindfulness training as an intervention for fibromyalgia: Evidence of post-intervention and 3-year follow-up benefits in well-being. Psychother Psychosom. 2007;76(4):226-33.
87. Pedersen SS, Denollet J, van Gestel YR, Serruys PW, van Domburg RT. Clustering of psychosocial risk factors enhances the risk of depressive symptoms 12-months post percutaneous coronary intervention. Eur J Cardiovasc Prev Rehabil. 2008;15(2):203-9.
88. Denollet J, Strik JJ, Lousberg R, Honig A. Recognizing increased risk of depressive comorbidity after myocardial infarction: Looking for 4 symptoms of anxiety-depression. Psychother Psychosom. 2006;75(6):346-52.
89. de Jonge P, van den Brink RHS, Spijkerman TA, Ormel J. Only incident depressive episodes after myocardial infarction are associated with new cardiovascular events. J Am Coll Cardiol. 2006;48(11):2204-8.
90. Carney RM, Freedland KE, Steinmeyer B, Blumenthal JA, de Jonge P, Davidson KW, et al. History of depression and survival after acute myocardial infarction. Psychosom Med. 2009;71(3):253-9.
91. Bush DE, Ziegelstein RC, Tayback M, Richter D, Stevens S, Zahalsky H, et al. Even minimal symptoms of depression increase mortality risk after acute myocardial infarction. Am J Cardiol. 2001;88(4):337-41.

Nederlandse samenvatting (Dutch summary)

Op dit moment leven meer dan 1 miljoen mensen in Nederland met een hart- of vaatziekte en bijna 1 op de 3 Nederlanders overlijdt aan deze ziekte. Coronaire hartziekten (CHZ), zoals een acuut hartinfarct, zijn de meest voorkomende vormen van hart- en vaatziekten. CHZ zijn aandoeningen die worden veroorzaakt door afwijkingen in de kransslagaderen, de slagaderen die het hart van bloed en zuurstof voorzien. Door een ziekteproces dat slagaderverkalking, ofwel "atherosclerose", genoemd wordt, kunnen vettige, verkalkte ophopingen in de wand van een kransslagader ontstaan (plaques) waardoor deze vernauwd raakt, wat kan leiden tot pijn op de borst. Een zogenaamde "atherosclerotische plaque" kan vervolgens openbarsten, waardoor de inhoud ervan in de bloedbaan terecht komt en bloedstolselvorming optreedt. Wanneer een kransslagader door dit proces volledig afgesloten wordt, kan een acuut hartinfarct ontstaan. Hoewel de kans op overlijden aan CHZ in de afgelopen jaren is gedaald – met name dankzij verbeterde behandelmogelijkheden - zijn CHZ nog steeds één van de belangrijkste oorzaken van overlijden en ziekte wereldwijd en doen daarmee een groot beroep op de gezondheidszorg.

Naast medicatie zijn een dotterbehandeling (PCI) of bypassoperatie (CABG) de meest gebruikte methoden om vernauwde of verstopte kransslagaderen te behandelen en de bloedtoevoer naar het hart te herstellen bij CHZ patiënten. Tijdens een dotterbehandeling wordt via een katheter een ballonnetje in de vernauwde of verstopte kransslagader gebracht en opgeblazen om de slagader te openen. Om ervoor te zorgen dat de kransslagader open blijft en de kans op het terugkeren van een vernauwing of verstopping te verkleinen, wordt tevens een zogenaamde stent geplaatst: een cilindervormige gaasstructuur met een doorsnede die gelijk is aan het bloedvat. Om het risico op een nieuwe vernauwing nog meer te verkleinen, worden er sinds 2001 stents gebruikt die medicijnen afgeven, de zogenaamde "drug-eluting stents". De meer invasieve bypassoperatie is een openhartoperatie, waarbij de vernauwing of verstopping in de kransslagader wordt omzeild door het aanleggen van een "omleiding". Een "gezonde" slagader, meestal uit de borstkas of het been, wordt gebruikt om een nieuwe vaatverbinding te maken en zo de bloedtoevoer naar het hart te herstellen.

Aanvankelijk werd een dotterbehandeling vooral toegepast bij patiënten met vernauwingen of verstoppingen in slechts 1 kransslagader, terwijl bypassoperaties werden toegepast bij patiënten met complexere problemen. In de loop der jaren is veel ervaring opgebouwd met het toepassen van dotterbehandelingen, is de techniek verbeterd en zijn medicijnen ontwikkeld die de schadelijke gevolgen van procedure-gerelateerde complicaties beperken, waardoor het indicatiegebied voor dotterbehandelingen kon worden uitgebreid: in 2012 ondergingen 45.305 patiënten in Nederland een dotterbehandeling, vergeleken met 11.240 bypassoperaties in datzelfde jaar.

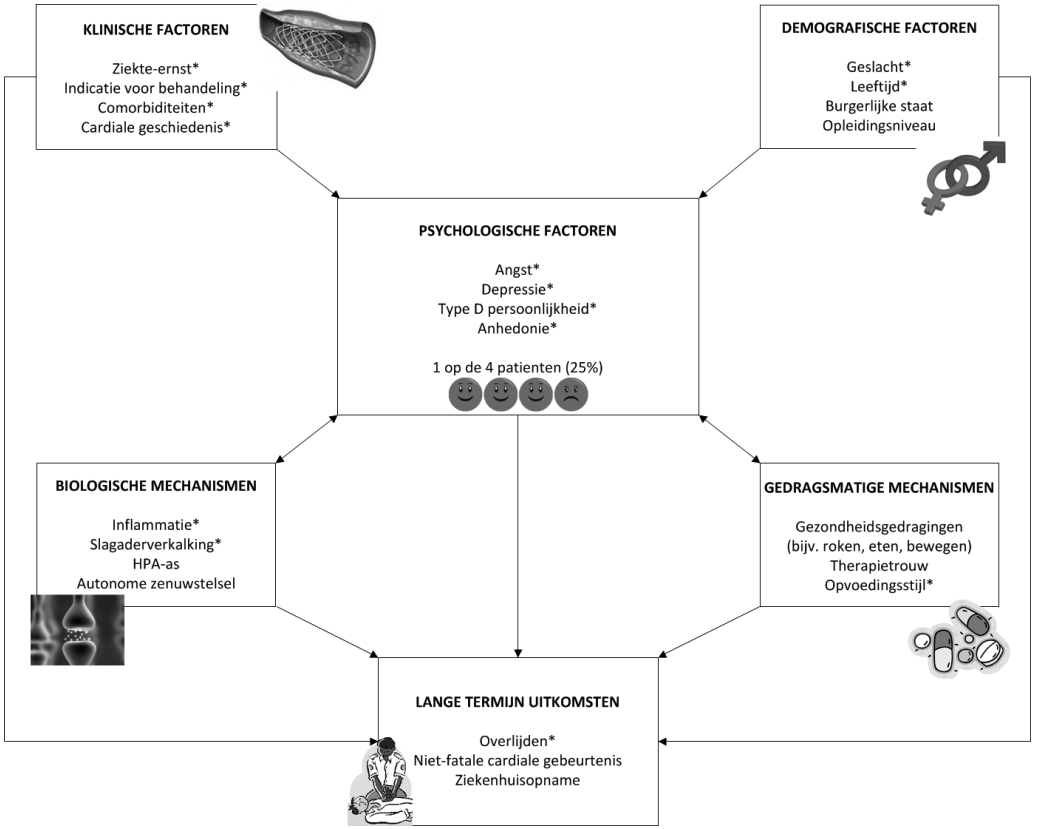
Er zijn verschillende risicofactoren voor het ontstaan van CHZ bekend, zoals roken, suikerziekte, een hoog cholesterol gehalte en een hoge bloeddruk. Deze factoren kunnen ook het ziektebeloop (de prognose) bij patiënten die al CHZ hebben verslechteren. De laatste jaren is er steeds meer aandacht voor de rol van psychologische factoren, zoals angst, depressie en Type D persoonlijkheid. Type D persoonlijkheid wordt gekenmerkt door de gelijktijdige aanwezigheid van 2 persoonlijkheidskenmerken: negatieve affectiviteit en sociale inhibitie. Met andere woorden, patiënten met een Type D persoonlijkheid (ook wel "binnenvetters" genoemd) ervaren veel verschillende negatieve emoties, maar zijn niet geneigd deze te uiten in sociale situaties uit angst voor afwijzing of afkeuring door anderen. Uit eerdere onderzoeken blijkt dat psychische klachten, zoals angst, depressie en Type D persoonlijkheid, voorkomen bij ongeveer 1 op de 4 CHZ patiënten en dat deze het ziektebeloop negatief kunnen beïnvloeden. Zo hebben CHZ patiënten die psychische klachten ervaren een verhoogd risico op vroegtijdig overlijden en ziekenhuisopnames en rapporteren zij een lagere kwaliteit van leven.

DOEL VAN DIT PROEFSCHRIFT

De meeste onderzoeken die tot nu toe gedaan zijn naar de invloed van psychologische factoren op de prognose van patiënten met CHZ, hebben zich gericht op patiënten die een bypassoperatie hebben ondergaan of op hartinfarctpatiënten. De rol van psychologische factoren bij patiënten die een dotterbehandeling ondergaan is tot nu toe onderbelicht gebleven. Komen psychische klachten net zo vaak voor bij dotterpatiënten als bij andere groepen hartpatiënten of bestaan er verschillen? Welke factoren dragen bij aan het ontstaan van psychische klachten bij dotterpatiënten? Wat is de invloed van psychologische factoren op de langetermijnprognose van dotterpatiënten? Deze vragen staan centraal in dit proefschrift.

Figuur 1 geeft een overzicht van demografische, klinische en psychologische factoren die mogelijk een rol spelen bij het ziektebeloop van CHZ patiënten, gebaseerd op eerder onderzoek. In dit proefschrift wordt onderzocht in hoeverre enkele van deze factoren en relaties ook aanwezig zijn bij patiënten die een dotterbehandeling hebben ondergaan.

Figuur 1. Klinische, demografische en psychologische factoren die (mogelijk) samenhangen met het ziektebeloop van CHZ patiënten



VOORNAAMSTE BEVINDINGEN VAN DIT PROEFSCHRIFT

Met uitzondering van hoofdstuk 10, zijn alle onderzoeken in dit proefschrift gebaseerd op gegevens verzameld bij patiënten die gedotterd zijn in het Erasmus MC in Rotterdam. Op verschillende momenten na de dotterbehandeling zijn vragenlijsten afgenomen, waarmee informatie is verkregen over demografische, klinische en psychologische kenmerken van deze patiënten. Hoofdstuk 10 is gebaseerd op data die verkregen is uit nationale registers in Denemarken.

Zowel (min of meer chronische) pijn op de borst als een hartinfarct kunnen indicaties zijn voor een dotterbehandeling. Vanwege het meer acute karakter van een hartinfarct, wordt vaak gedacht dat deze patiënten meer psychische klachten ervaren na een dotterbehandeling dan patiënten die gedotterd worden naar aanleiding van klachten van pijn op de borst. Echter, uit de resultaten van **hoofdstuk 2** van dit proefschrift blijkt dat er geen relevante verschillen zijn in de mate van angst en depressie tussen patiënten die gedotterd zijn na het doormaken van een hartinfarct of naar aanleiding van pijn op de borst.

Hoofdstuk 3 beschrijft het beloop van angst en depressie over tijd in dotterpatiënten. Uit dit onderzoek blijkt dat angst en depressie bij ongeveer 80% van de patiënten stabiel blijven, tot een jaar na de dotterbehandeling. Wanneer patiënten ten tijde van de dotterbehandeling klachten van angst en depressie ervaren, bestaat er dus een grote kans dat deze klachten een jaar na de behandeling nog steeds bestaan. Anderzijds, wanneer patiënten ten tijde van de dotterbehandeling geen psychische klachten ervaren, is de kans groot dat zij geen klachten van angst en depressie ontwikkelen.

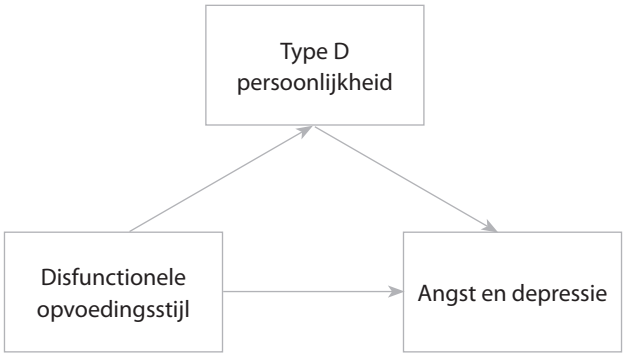
Zoals eerder beschreven is er bij patiënten met CHZ veel onderzoek gedaan naar de invloed van psychologische factoren op de prognose van patiënten. Een klein aantal van deze onderzoeken heeft onderzocht of depressie ook de langetermijnprognose beïnvloedt, maar resultaten van deze onderzoeken zijn wisselend. Uit de bevindingen van **hoofdstuk 4** blijkt dat depressie voorkomt bij 26% van de dotterpatiënten en dat patiënten die depressieve klachten ervaren ten tijde van de dotterbehandeling een 50% hogere kans hebben om te overlijden na 7 jaar, dan patiënten zonder depressieve klachten. Tevens toont dit onderzoek aan dat het effect van depressie op overlijden onafhankelijk is van andere psychologische factoren, zoals angst en Type D persoonlijkheid. Zowel angst als Type D persoonlijkheid komen in dit onderzoek bij 29% van de dotterpatiënten voor.

Binnen het onderzoek naar de rol van psychologische factoren bij CHZ wordt voornamelijk aandacht geschonken aan de rol van negatieve emoties, zoals angst en depressie. Over de invloed van positieve emoties is veel minder bekend. Enkele onderzoeken hebben zich gericht op de rol van anhedonie, ofwel het gebrek aan het ervaren van positieve emoties, in CHZ. Uit de resultaten van deze onderzoeken blijkt dat patiënten met anhedonie een hoger risico hebben op overlijden binnen 2 jaar na een cardiale gebeurtenis (zoals een hartinfarct) en een lagere kwaliteit van leven rapporteren, dan patiënten zonder anhedonie. De invloed van anhedonie op de langetermijnprognose is nog niet eerder onderzocht. **Hoofdstuk 5** richt zich op de vraag of anhedonie invloed heeft op de langetermijnsterfte onder dotterpatiënten. De resultaten van dit onderzoek laten zien dat anhedonie voorkomt bij 24% van de dotterpatiënten en dat patiënten met anhedonie klachten ten tijde van de dotterbehandeling een 60% hogere kans hebben om te overlijden na 7 jaar, in vergelijking met patiënten zonder anhedonie klachten.

Uit eerdere onderzoeken blijkt dat de invloed van obesitas (BMI >30) op overlijden in CHZ patiënten paradoxaal is: mensen met obesitas overlijden minder snel dan mensen met een gezond gewicht. De verklaring voor dit fenomeen is tot op heden onbekend. In **hoofdstuk 6** wordt onderzocht of er bij dotterpatiënten ook sprake is van deze zogenaamde "obesitas paradox" en of de gezondheidstoestand van patiënten hiervoor een mogelijke verklaring kan bieden. Gezondheidstoestand wordt gedefinieerd als de "perceptie van de patiënt met betrekking tot de invloed van een ziekte of behandeling op zijn of haar symptomen, functioneren en kwaliteit van leven". Het zou zo kunnen zijn dat obese patienten een betere gezondheidstoestand rapporteren dan niet-obese patienten en dat dit mogelijk leidt tot een betere prognose. Uit dit onderzoek blijkt dat patiënten met overgewicht (BMI 25-30), maar *niet* de obese patiënten, een 40% lager risico hebben om te overlijden 7 jaar na de dotterbehandeling, in vergelijking met patiënten met een gezond gewicht (BMI 18.5-25). Er lijkt dus geen sprake van een obesitas paradox, maar wel van een "overgewicht paradox". Uit het onderzoek blijkt ook dat de patiëntgerapporteerde gezondheidstoestand geen verklaring biedt voor deze paradox.

In **hoofdstuk 7** staat de relatie tussen opvoedingsstijl, angst en depressie en Type D persoonlijkheid centraal. Uit de bevindingen blijkt dat een overbezorgde of verwaarlozende opvoedingsstijl door ouders (zoals herinnerd door patiënten) samenhangt met angst, depressie en Type D persoonlijkheid bij patiënten die een dotterbehandeling hebben ondergaan. Op basis van de resultaten wordt gesuggereerd dat een disfunctionele opvoedingsstijl kan bijdragen aan het ontstaan van een Type D persoonlijkheidstype en dat dit vervolgens kan leiden tot verhoogde angst en depressie (Figuur 2). Echter, deze hypothese moet verder worden onderzocht.

Figuur 2. Samenhang tussen disfunctionele opvoedingsstijl, angst en depressie en Type D persoonlijkheid



Verschillende onderzoeken hebben zich gericht op mogelijke biologische en gedragsmatige mechanismen die de relatie tussen psychische klachten en de prognose van CHZ patiënten kunnen verklaren (zie ook Figuur 1). Vaak onderzochte biologische mechanismen zijn inflammatie en de mate van atherosclerose (slagaderverkalking). Inflammatie is een verzamelnaam voor de afweerreactie van het lichaam tegen vreemde organismen (zoals virussen en bacteriën) en treedt op bij verwonding en ziekte. De mate van inflammatie kan gemeten worden aan de hand van bepaalde markers in het bloed, de zogenaamde "cytokines". Zowel inflammatie als de mate van atherosclerose zijn gerelateerd aan het ontstaan en de progressie van CHZ. Eerder onderzoek heeft verbanden aangetoond tussen psychische klachten, zoals angst, depressie en Type D persoonlijkheid, en een verhoogde inflammatie in CHZ. Ook blijken psychische klachten samen te hangen met een verhoogde mate van atherosclerose. Echter, in andere studies werden deze relaties niet gevonden. In **hoofdstuk 8** worden inflammatie en de mate van atherosclerose onderzocht als mogelijke verklaringen voor de relatie tussen psychische klachten en prognose bij patiënten die een dotterbehandeling hebben ondergaan. In dit hoofdstuk worden geen duidelijke verbanden gevonden tussen psychische klachten en inflammatie of de mate van atherosclerose, dus deze beide mechanismen lijken bij dotterpatiënten geen belangrijke rol te spelen. Mogelijk spelen andere, meer gedragsmatige, mechanismen een grotere rol in deze patiëntengroep, maar meer onderzoek op dit gebied is nodig.

In **hoofdstuk 9** wordt het fenomeen "attritie-bias" onderzocht in een prospectieve studie bij dotterpatiënten. Er is sprake van een mogelijke attritie-bias in een wetenschappelijk onderzoek als studiedeelnemers die het onderzoek helemaal afronden verschillen

van deelnemers die voortijdig uitvallen ("uitvallers"), waardoor de resultaten van het onderzoek mogelijk vertekend kunnen worden. Uit hoofdstuk 9 blijkt dat er inderdaad verschillen bestaan tussen patiënten die zowel een maand als een jaar na de dotterbehandeling de vragenlijsten hebben ingevuld en patiënten die dit wel een maand na de dotterbehandeling hebben gedaan, maar niet na een jaar (uitvallers). De uitvallers zijn jonger, roken vaker, maar krijgen minder vaak bepaalde hartmedicijnen voorgeschreven (calcium-antagonisten en ACE-remmers), in vergelijking met patiënten die op beide momenten de vragenlijsten hebben ingevuld. Daarnaast ervaren uitvallers vaker psychische klachten, zoals angst en depressie. Tot slot is onderzocht of uitvallers een slechtere prognose hebben en eerder overlijden dan patiënten die de gehele onderzoeksduur betrokken blijven bij het onderzoek, maar hierin zijn geen verschillen gevonden. De resultaten van dit onderzoek suggereren dat het in vervolgonderzoeken zinvol is om aandacht te besteden aan deze zogenoemde attritie-bias en er bij stil te staan dat dit mogelijk de bevindingen van een onderzoek kan vertekenen.

Tot slot is in **hoofdstuk 10** het nationale Deense Hart Register gebruikt om informatie op te vragen over alle patiënten die tussen 1999 en 2012 opgenomen zijn geweest in een Deens ziekenhuis en een dotterbehandeling of bypassoperatie hebben ondergaan. Daarnaast is informatie opgevraagd met betrekking tot het gebruik van medicatie voor angst en depressie (anxiolytica en antidepressiva) in beide patiëntengroepen, tot aan een jaar na de behandeling. Uit dit onderzoek blijkt dat er geen klinisch relevante verschillen bestaan in het gebruik van antidepressiva en anxiolytica tussen patiënten die gedotterd zijn en patiënten die een bypassoperatie hebben ondergaan. Deze bevindingen duiden er mogelijk op dat er geen grote verschillen bestaan in de mate waarin zij klachten van angst en depressie ervaren, maar meer onderzoek op dit gebied is nodig.

CONCLUSIES EN AANBEVELINGEN

Een dotterbehandeling wordt in vergelijking met een bypassoperatie doorgaans beschouwd als een niet-invasieve procedure, waarbij na de behandeling meestal meteen een verbetering in lichamelijke klachten, zoals benauwdheid en vermoeidheid, optreedt. Echter, de resultaten van dit proefschrift suggereren dat niet alleen de medische situatie met betrekking tot de kransslagaderen van belang is voor het welbevinden van dotterpatiënten, maar dat ook psychologische factoren een rol spelen. Uit dit proefschrift blijkt namelijk dat psychische klachten, zoals angst, depressie en Type D persoonlijkheid, voorkomen bij 25-29% van de dotterpatiënten. Deze percentages komen overeen met bevindingen in andere CHZ groepen (zoals hartinfarctpatiënten en patiënten die een bypassoperatie hebben ondergaan). Hoewel de gevonden prevalentie van psychische

klachten in de onderzoeken dus vrij hoog is, zou dit toch nog een onderschatting kunnen zijn gezien het feit dat patiënten met psychische klachten minder geneigd zijn mee te doen aan onderzoek of, zoals aangetoond in dit proefschrift, vaker voortijdig uitvallen (attritie-bias) dan patiënten zonder psychische klachten.

Bij de meerderheid van de dotterpatiënten (ongeveer 80%) blijven psychische klachten stabiel over tijd: wanneer patiënten ten tijde van de dotterbehandeling psychische klachten ervaren, bestaat er een grote kans dat deze klachten een jaar na de behandeling nog steeds aanwezig zijn. De resultaten in dit proefschrift laten verder zien dat het ervaren van psychische klachten na een cardiale gebeurtenis niet zozeer samenhangt met ziekte-ernst, type behandeling (dotterbehandeling vs. bypassoperatie) of de indicatie voor behandeling (hartinfarct vs. pijn op de borst), maar meer met psychologische factoren die relateren aan de "subjectieve ervaring" van de hartziekte. Zo blijkt dat het ervaren van psychische klachten na een dotterbehandeling vooral voorspeld wordt door het wel of niet aanwezig zijn van deze klachten ten tijde van de behandeling. Daarnaast lijkt er een positief verband te bestaan tussen Type D persoonlijkheid en het ervaren van angst en depressie bij dotterpatiënten. Uit dit proefschrift blijkt tevens dat dotterpatiënten met klachten als depressie en anhedonie een slechtere langetermijnprognose hebben en eerder overlijden dan patiënten zonder deze klachten. Tot slot suggereren de resultaten dat inflammatie en de mate van atherosclerose geen duidelijke verklaring bieden voor de samenhang tussen psychische klachten en prognose bij dotterpatiënten; mogelijk spelen meer gedragsmatige mechanismen een grotere rol in deze patiëntengroep.

Om de zorg voor dotterpatiënten in de klinische praktijk te optimaliseren, is het dus van belang om niet alleen aandacht te besteden aan medische factoren, zoals ziekte-ernst, maar ook het psychologisch welbevinden van dotterpatiënten in ogenschouw te nemen. Hartrevalidatie is een belangrijke vorm van nazorg voor patiënten met CHZ, waarin fysieke training gecombineerd wordt met leefstijladviezen en psychologische begeleiding. Het is bekend dat het volgen van een hartrevalidatie programma na een cardiale gebeurtenis positieve effecten heeft en kan zorgen voor een vermindering van psychische klachten, een betere kwaliteit van leven en een gunstigere prognose. Echter, uit onderzoek blijkt dat meer dan één derde van de patiënten die een dotterbehandeling heeft ondergaan *niet* deelneemt aan een hartrevalidatie programma. Daarnaast is de uitval in hartrevalidatieprogramma's hoog, waarbij vooral patiënten uitvallen die het mogelijk het hardst nodig hebben, zoals patiënten die angst en depressie ervaren en een lage kwaliteit van leven rapporteren. Het is dus zinvol om patiënten met psychische klachten in een vroegtijdig stadium te identificeren en gepaste nazorg te bieden, eventueel in de vorm van een aanvullende psychologische behandeling, toegespitst op de behoeften en voorkeuren van de individuele patiënt.

Dankwoord
(Acknowledgements)

DANKWOORD

Het duurt even een paar jaar, maar dan heb je ook wat: het proefschrift is klaar! Via deze weg wil ik een aantal mensen bedanken die hebben bijgedragen aan de totstandkoming van dit boekje.

Allereerst wil ik alle patiënten bedanken die hebben meegewerkt aan de verschillende studies van dit proefschrift. Bedankt voor jullie bereidheid om alle vragenlijsten in te vullen, zonder jullie bijdrage was dit proefschrift er nooit geweest!

Ook gaat mijn dank uit naar mijn promotoren: Prof. dr. Susanne Pedersen en Prof. dr. Eric Boersma en mijn copromotor dr. Henneke Versteeg. Bedankt voor jullie fijne begeleiding en voor alles wat jullie mij geleerd hebben. Jullie enthousiasme voor de wetenschap werkt aanstekelijk! Ik mag dan misschien niet zo in de wieg gelegd zijn als "praat-psycholoog", maar mijn enthousiasme voor het onderzoek is dankzij jullie des te groter geworden.

Susanne, bedankt dat je me ruim 3 jaar geleden de kans bood om bij jou als AIO aan de slag te gaan. Ik heb onze samenwerking als erg prettig ervaren en heb ontzettend veel van je geleerd! Bedankt voor het vertrouwen dat je altijd in me gehad hebt en voor het feit dat ik altijd bij je terecht kon, zowel op werk als op persoonlijk vlak. Ik ben blij dat ik jou op mijn beurt af en toe wat Didi-kleding aan heb kunnen smeren :-). Ik vind het knap dat je de stap hebt gemaakt om naar Denemarken te gaan en wens je daar alle goeds. Ik hoop dat we in de toekomst nog regelmatig een "Chardonnaytje" met elkaar kunnen drinken en wellicht nog eens een bezoekje kunnen brengen aan jouw geliefde Christiania in Kopenhagen?!

Eric, dank je wel voor je begeleiding vanuit het Erasmus MC. Ik vind het fijn dat jouw deur altijd voor me open stond en ik heb veel van je geleerd. Jouw kritische blik hielp me om dingen soms net vanuit een ander perspectief te zien, wat mijn proefschrift zeker ten goede is gekomen!

Henneke, mijn allerliefste roomie, wat hebben we samen een leuke tijd gehad op de universiteit: In P604 was het altijd een feestje!. Bedankt voor je begeleiding bij mijn proefschrift, ik vind het heel fijn dat ik altijd bij je terecht kon met mijn vragen, al was het maar om soms alleen even te horen "ja dat is goed" :-). Ik wil je ook heel erg bedanken voor alle gezelligheid buiten de universiteit, zoals tijdens congressen of onze vele etentjes en borrelavondjes. Ik ben heel blij met jouw vriendschap en zou je niet meer kunnen missen!

Aline, zonder jou was ik nooit als AIO op de universiteit terecht gekomen. Bedankt dat je me tijdens mijn afstudeerstage kennis hebt laten maken met wat een promotieonderzoek inhoudt en dat je me aan deze baan hebt geholpen. Jouw fijne begeleiding tijdens mijn eerste jaar zorgde ervoor dat ik me al snel thuis voelde op de

universiteit. Ook zal ik mijn eerste congres in Brussel nooit vergeten, waarbij ik mijn "spa rood sur les montagnes" heel charmant over jullie uitspuugde omdat ik zo moest lachen om jou!

Johan, bedankt voor de fijne tijd op de afdeling en je betrokkenheid bij een aantal van mijn artikelen. Ik heb bewondering voor jouw eindeloze kennis over tal van onderwerpen en heb daar veel van geleerd. Ik hoop dat onze wegen elkaar in de toekomst nog eens zullen kruisen!

Verder wil ik graag mijn promotiecommissie bedanken, bestaande uit Prof. dr. Guus van Heck, Prof. dr. Victor Pop, Prof. dr. Felix Zijlstra, dr. Christina Bode, dr. Nina Kupper en dr. Ken Redekop. Bedankt voor jullie bereidheid zitting te nemen in mijn promotiecommissie en mijn proefschrift te beoordelen. Christina, het ARPH congres dat we samen in Twente hebben georganiseerd zal ik nooit vergeten! Ons motto "als jij er niet aan hebt gedacht en ik ook niet, dan zal het wel niet belangrijk zijn" heeft het congres tot een waar succes gemaakt! Bedankt dat je deur altijd voor me open stond in Twente en ik hoop dat we elkaar in de toekomst nog regelmatig zullen blijven zien.

De interventiecardiologen van het Thoraxcentrum van het Erasmus MC wil ik bedanken voor het feit dat ik heb mogen werken met databestanden gebaseerd op jullie patiënten. Ron, bedankt voor het ter beschikking stellen van de data en je feedback op mijn artikelen. Ook de overige coauteurs wil ik bedanken voor hun kritische en waardevolle feedback op mijn manuscripten.

Gunnar and Stefan, thank you for your kind hospitality and supervision during our stay in Copenhagen. Although SAS and STATA sometimes "drove us crazy", we had a wonderful time!

Remco, bedankt dat jij het ontwerp voor de cover van dit proefschrift en de uitnodigingen hebt willen verzorgen. Fijn dat jij na 3 zinnen wist wat ik ongeveer voor ogen had! Als het van mijn eigen creativiteit af had moeten hangen, was het waarschijnlijk een heel saai boekje geworden. Sean, bedankt voor je bereidheid om ondanks je eigen drukke agenda de lay-out van mijn proefschrift te verzorgen en mijn "correctiebijbeltjes" en "beschouwingen" te verwerken. Zonder jullie beide had dit proefschrift er nooit zo mooi uitgezien, ik ben erg blij met het eindresultaat!

Mijn ex-collega's van Tilburg University en het Erasmus MC wil ik graag bedanken voor de fijne samenwerking van de afgelopen jaren. In het bijzonder wil ik de "device-ladies" Corline, Henneke, Madelein, Mirjam en Mirela bedanken voor alle fijne en leuke momenten op de universiteit en daarbuiten, ik ben blij dat jullie mij als "niet-device-AIO" wilden adopteren. Mirjam, ik heb genoten van onze gezamenlijke congressen in Parijs en Bordeaux. Corline, bedankt voor de supertijd die we samen in Kopenhagen hebben gehad! Bewoners van de 6e verdieping, de gezellige lunches en borrels op onze "party-gang" waren onvergetelijk! Bedankt voor alle gezelligheid en het luisterend oor wat ik

altijd bij jullie vond, ik ga jullie missen!

Ik wil mijn collega's van het NIVEL bedanken voor de warme ontvangst. In het bijzonder mijn leidinggevende Prof. dr. Cordula Wagner en mijn "mede-patiëntveiligheid-collega's": ik heb veel zin om aan mijn nieuwe project te gaan beginnen en ik kijk uit naar onze verdere samenwerking! Kamergenootjes Sanneke, Stef en Paul, bedankt voor het beantwoorden van de vele vragen op mijn eerste dagen, mede dankzij jullie voelde ik me al gauw thuis binnen het NIVEL!

Lieve Saar en Miep, ik ben heel erg blij dat jullie als paranimfen achter me staan, ik had me geen betere "nimfjes" kunnen wensen! Met jullie talloze one-liners over het hart weet ik zeker dat het met die verdediging wel goed gaat komen, jullie hebben het hart op de juiste plek zitten! Nu maar hopen dat ik niet ziek wordt…

Saar, ik ken je zo ongeveer al mijn hele leven en van kleins af aan hebben we lief en leed gedeeld. Over wat wij allemaal samen hebben meegemaakt, zou ik een boek kunnen schrijven! Stapavondjes, shoppen, sauna, concerten, weekendjes weg, mooie reizen en vooral uren en uren kletsen over alles wat ons bezighoudt. Bedankt dat je er altijd voor me bent, ook al vertel ik 10x hetzelfde verhaal. Ik kijk uit naar alle dingen die we samen nog gaan meemaken, met om te beginnen een mooie reis in het najaar. Je bent een super vriendin!

Marieke, miepie, gompie, jouw beslissing om een master in Tilburg te gaan volgen en bij ons in "huisje-boompje-feestje" te komen wonen is wat mij betreft één van de beste uit je leven geweest, want ik zou je nooit meer kunnen missen! Ook al wonen we niet meer in hetzelfde huis, we spreken elkaar bijna dagelijks en delen elk klein detail van ons leven. Voordat ik het zelf weet, weet jij vaak al hoe ik me voel of ergens over denk... zo bijzonder! Fijn dat jij me er zo nu en dan op wijst dat ik ook wel eens de stoptrein kan pakken :-). Ik geniet enorm van onze vriendschap, alle leuke dingen die we samen doen en onze eindeloze gesprekken (met name over eten). Weet dat ik heel erg trots op je ben!

Lieve Mark, vanaf het moment dat wij elkaar hebben ontmoet in de TIK-week zijn we onafscheidelijk. Jij hebt mijn studententijd in Tilburg tot een onvergetelijke tijd gemaakt! Ik ben je ontzettend dankbaar voor het feit dat je nooit te beroerd was om me af te melden voor college als "Dikkie Laurina Mathilda Damen". Maar de kers op de taart van onze avonturen is toch wel de fantastische tijd die we in Zuid-Afrika hebben gehad! Wat hebben we daar veel leuke dingen gedaan en wat was het fijn om dat samen met jou te delen! Ik ben heel blij met jou als mijn maatje en ik hoop dat we in de toekomst nog veel mooie momenten samen zullen meemaken, met meer vals spelen tijdens een potje Tai-pan, meer wijn en meer borrelhapjes!

Lieve Lon, zonder jou zou het leven er een stuk saaier uitzien! Wat begon als een onzeker "Papa, mag Lonneke misschien bij mij komen spelen na de hockey?" is uitgegroeid tot een hechte vriendschap. Bedankt voor alle fijne en gezellige momenten die we samen

hebben meegemaakt. Vooral van de avonden dat we zeker-weten-op-stap-gaan-maar-uiteindelijk-toch-op-de-bank-belanden geniet ik volop! Ook op winkelgebied vullen wij elkaar naadloos aan en stoken we elkaar altijd heerlijk op om dingen te kopen die we van tevoren niet van plan waren :-). Bedankt dat ik altijd met mijn verhalen bij je terecht kan, ik vind je een super vriendin!

HKGD, ofwel Els, Renske, Roos en Terri, bedankt voor alle DOLFijne dingen die we met elkaar hebben beleefd tijdens de studie en daarna. Ik geniet erg van onze gezellige uitjes, zoals high tea'en, high wine'en, sinterkerst vieren en natuurlijk onze DOLdwaze weekendjes weg!

"Etten-Leur gang", Saar, Soof, Anja en Kaat, we go waaaaaaay back! Ik vind het heel erg leuk dat we elkaar nog altijd weten te vinden en zoveel gezellige dingen met elkaar doen. Ik zeg, dat houden we erin!

Annefleur, een potje tennissen in Goirle leidde tot het volledig uitstippelen van jouw leven, met gezellig samen werken op de uni, gezellig samen in een tennisteam en wie weet ooit nog gezellig als buufies naast elkaar wonen ;-). Bedankt voor de lol die we altijd samen hebben, op of buiten de tennisbaan, maar ook voor de serieuze gesprekken die we zo nu en dan ook nog wel eens voeren :-).

Maria, bedankt voor de jarenlange gezelligheid in ons huisje aan de Prof. Cobbenhagenlaan. Ik zal alle series die wij samen hebben gekeken, wijntjes en wodka-limes die we hebben gedronken en de "couple of M&M's" die we hebben gegeten, niet snel vergeten!

Ingrid en Margo, ik ben blij met jullie als mijn liebe grosse Schwestern! Een wintersport met jullie staat garant voor heel veel gemutlichkeit….en owja, af en toe ook wat skiplezier! Weet dat kleine Schwester altijd klaarstaat om jullie om 7.30u uit bed te trommelen en natuurlijk om Drei Grosse Bier te halen!

Cindy, mijn andere grote zus, ik vind het bijzonder hoeveel wij op elkaar lijken! Van jurkjes, jassen, schoenen, armbanden en huisinrichting tot aan het delen van gerechten in een restaurant…dit is meant to be! :-) Ik ben blij dat we elkaar hebben ontmoet en hoop dat we elkaar veel zullen blijven zien!

Lieve papa en mama, alias "de zwervertjes", bedankt dat jullie altijd voor me klaarstaan. Jullie vormen samen de ideale combi: Mama, bedankt dat ik bij jou altijd terecht kan met dingen waar "wij vrouwen" ons nou eenmaal soms druk om maken. Papa, jouw nuchtere kijk op het leven zorgt ervoor dat ik met beide benen op de grond blijf, bedankt dat je me altijd met raad en daad bijstaat! Wie had gedacht je ook nog eens kijk op mode had ;-). Ik heb veel bewondering voor hoe jullie in het leven staan en ik hoop dat jullie de komende jaren lekker blijven genieten en rondzwerven over de wereld, laat dat werken maar aan ons over! Ad en Elly, bedankt dat jullie er altijd voor Stijn en mij zijn, ik had me geen leukere en lievere schoonouders kunnen wensen!

Pim, lief klein broertje, inmiddels toren je hoog boven me uit en ligt de tijd dat ik volop over jou kon moederen ver achter ons (al probeer ik dat soms natuurlijk stiekem toch nog even :-)). Ik ben blij dat onze familie over een heuse "Dokter Mc Dreamy-in spe" beschikt, weet dat ik erg trots op je ben!

Lieve opa en oma, ik ben er trots op dat jullie bij mijn promotie aanwezig zijn! Speciaal voor jullie nu ook een deel van het boekje in het Nederlands, zodat jullie meer kunnen lezen dan alleen de namen van de referenties. En ja…ik heb het allemaal zelf geschreven! ;-)

En tot slot lieve, lieve Stijn, wat zou ik toch zonder jou moeten?! Je eindeloze geduld en gevoel voor humor in combinatie met je fantastische skills om knopen aan te zetten, de lekkerste maaltijden op tafel te toveren en klusjes in huis te doen ("Stijn, wil je even komen, het lukt niet") maken jou tot de beste en liefste vriend die ik me maar kan wensen! Bedankt dat je er altijd voor me bent en ik hoop dat ik ooit je droom om huisman te worden uit kan laten komen :-). Ik houd van je!

Nikki, februari 2014

List of publications
(Publicatielijst)

PUBLICATIONS

Damen NL, Brouwers CJ, Versteeg H, Christensen SB, Torp-Pedersen C, Gislason GH, Pedersen SS. Anti-depressant and anxiolytic medication use in patients treated with coronary artery bypass graft surgery versus percutaneous coronary intervention: A Danish nationwide population-based study. *Submitted for publication.*

Damen NL, Versteeg H, Mommersteeg PMC, Cheng JM, Garcia-Garcia HM, De Jaegere PP, Van Domburg RT, Pedersen SS, Boersma E. Psychological distress, inflammation, and IVUS plaque burden in patients treated with percutaneous coronary intervention. *Submitted for publication.*

Brouwers CJ, Christensen SB, **Damen NL,** Denollet J, Torp-Pedersen C, Gislason GH, Pedersen SS. Anti-depressant use and risk for mortality in 120,443 heart failure patients with or without a diagnosis of clinical depression. *Submitted for publication.*

Damen NL, Versteeg H, Van Helmondt SJ, De Jaegere PP, Van Geuns RM, Meine MM, Van Domburg RT, Pedersen SS. The distressed (Type D) personality mediates the relationship between remembered parenting and psychological distress in cardiac patients. Psychol Health. 2014;29(3):318-33.

Damen NL, Versteeg H, Serruys PW, Van Geuns RM, Van Domburg RT, Pedersen SS, Boersma E. Cardiac patients who completed a longitudinal psychosocial study had a different clinical and psychosocial baseline profile than patients who dropped out prematurely. Eur J Prev Cardiol. 2013; In press, doi: 10.1177/2047487313506548.

Damen NL, Versteeg H, Boersma E, de Jaegere PP, van Geuns RM, van Domburg RT, Pedersen SS. Indication for percutaneous coronary intervention is not associated with symptoms of anxiety and depression. Int J Cardiol. 2013;168(5):4897-8.

Damen NL, Pedersen SS. In reply to the Letter to the Editor of Dr. Kawada: "Depression and 7-year mortality for patients treated with percutaneous coronary intervention". Int J Cardiol. 2013;168(3):2880-1.

Damen NL, Versteeg H, Boersma E, Serruys PW, Van Geuns RM, Denollet J, van Domburg RT, Pedersen SS. Depression is independently associated with 7-year mortality in patients treated with percutaneous coronary intervention: Results from the RESEARCH registry. Int J Cardiol. 2013;167(6):2496-501.

Younge J, **Damen NL,** van Domburg RT, Pedersen SS. Obesity, health status, and 7-year mortality in percutaneous coronary intervention: In search of an explanation for the obesity paradox. Int J Cardiol. 2013;167(4):1154-8.

Damen NL, Pelle AJ, Boersma E, Serruys PW, van Domburg RT, Pedersen SS. Reduced positive affect (anhedonia) is independently associated with 7-year mortality in patients treated with percutaneous coronary intervention: Results from the RESEARCH registry. Eur J Prev Cardiol. 2013;20(1):127-34.

Damen NL, Pelle AJ, Szabó BM, Pedersen SS. Symptoms of anxiety and cardiac hospitalizations at 12 months in patients with heart failure. J Gen Intern Med. 2012;27(3):345-50.

Damen NL, Pelle AJ, Van Geuns RM, Van Domburg RT, Boersma E, Pedersen SS. Intra-individual changes in anxiety and depression during 12-month follow-up in percutaneaous coronary intervention patients. J Affect Disord. 2011;134(1–3):464-7.